CLINICAL STUDY PROTOCOL

Title:	A Phase 3, double-blind, randomized study of RVT-101 versus placebo when added to existing stable donepezil treatment in subjects with mild to moderate Alzheimer's disease
Sponsor	Axovant Sciences Ltd.
Compound Name:	RVT-101
Protocol Number	RVT-101-3001
Indication	Treatment of mild to moderate Alzheimer's disease in patients on stable therapy with donepezil
Development Phase	3
IND #	78,094
Version/ Date:	3.0 13 April 2016
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Confidentiality Statement

SPONSOR SIGNATURE PAGE

Study title: A Phase 3, double-blind, randomized study of RVT-101 versus placebo when added to existing stable donepezil treatment in subjects with mild to moderate Alzheimer's disease

Protocol Number: RVT-101-3001

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

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Apr 13, 2016

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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
ACh	acetylcholine
AChE	acetylcholinesterase
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADAS-Cog-11	Alzheimer's Disease Assessment Scale – Cognitive Subscale-11 items
ADAS-Cog-13	Alzheimer's Disease Assessment Scale – Cognitive Subscale-13 items (ADAS-Cog-11 plus delayed word recall and total digit cancellation tests)
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{\tau ss}$	area under the concentration-time curve at steady state
BUN	blood urea nitrogen
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CFR	Code of Federal Regulations
CI	confidence interval
CIBIC+	Clinician's Interview-Based Impression of Change – plus caregiver interview
CIBIS	Clinician's Interview-Based Impression of Severity
C_{max}	peak concentration
C_{max-ss}	peak concentration at steady state
C_{min}	minimum (trough) concentration
C_{min-ss}	minimum (trough) concentration at steady state
CNS	central nervous system
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
DS	Dependence Scale
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	EuroQOL 5 dimensions questionnaire
EQ-VAS	EuroQOL visual analogue scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HBsAg	hepatitis B surface antigen

Abbreviation	Definition
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
MAO	monoamine oxidase
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NMDA	N-methyl-D-aspartate
NPI	Neuropsychiatric Inventory
Pgp	permeability glycoprotein
PK	pharmacokinetic(s)
PP	per protocol
PSA-NCAM	polysialylated form of the neural cell adhesion molecule
QTc	corrected QT (interval)
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	red blood cell
RUD Lite	Resource Utilization in Dementia Lite
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WCT	Worldwide Clinical Trials
WHO	World Health Organization

2. PROTOCOL SUMMARY

Study Title	A Phase 3, double-blind, randomized study of RVT-101 versus placebo when added to existing stable donepezil treatment in subjects with mild to moderate Alzheimer's disease
Objectives	Primary • To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on cognitive function as measured by the Alzheimer's Disease Assessment Scale – Cognitive Subscale 11 items (ADAS-Cog-11) after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on activities of daily living as measured by the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) scale after 24 weeks of treatment Secondary • To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on cognition as measured by the ADAS-Cog-13 (ADAS-Cog-11 plus delayed word recall and total digit cancellation tests) after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on global clinical assessment of change as measured by Clinician's Interview-Based Impression of Change – plus caregiver interview (CIBIC+) after 24 weeks of treatment • To assess how baseline Mini Mental State Examination (MMSE) score severity affects efficacy outcome measures after 24 weeks of treatment. • To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory (NPI) after 24 weeks of treatment • To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on an analysis of responders based on prespecified efficacy evaluations • To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on subject dependency as measured by the Dependence Scale (DS) • To measure RVT-101 plasma concentrations and donepezil plasma concentrations in study subjects • To estimate the pharmacokinetic (PK) parameters of RVT-101 and donepezil and explore relationships to efficacy or safety endpoints, as appropriate • To assess the safety and tolerability of RVT-101 as an adjunct therapy to stable donepezil treatment Tertiary • To assess the effects of RVT-101 versus placebo as adjuncts to

	stable donepezil therapy on healthcare utilization as measured by the Resource Utilization in Dementia Lite (RUD Lite) • To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on quality of life as measured by the EuroQOL 5 dimensions questionnaire (EQ-5D)
Study Phase	Phase 3
Target Population	Adult subjects aged 50 to 85, inclusive, with mild to moderate Alzheimer's disease (AD). Subjects will be stratified by baseline MMSE score into 3 groups by severity.
Number of Subjects Planned	Approximately 1150 randomized subjects: RVT-101: 575 subjects Placebo: 575 subjects
Number of Study Centers Planned	Approximately 185
Study Design	This is a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in patients with mild to moderate AD who are on stable donepezil therapy. The efficacy and safety of RVT-101 at a dose of 35 mg daily when used as an adjunct treatment to stable donepezil therapy will be evaluated over a 24-week treatment period. All subjects will remain on stable doses of donepezil for the duration of the study. The randomization ratio will be 1:1 (RVT-101:placebo) and will be stratified by baseline MMSE score into 3 groups of severity.
Duration of Treatment	Study participation will last approximately 33 weeks: 0 to 28 days for Screening, a 3-week Single-Blind Run-In Period to evaluate baseline status, a 24-week randomized Double-Blind Treatment Period, and a 2-week Follow-Up Period (for subjects who do not enter the open-label extension study RVT-101-3002).
Criteria for Evaluation	Primary efficacy measures: The primary efficacy response will be an assessment of change at 24 weeks from baseline in cognition and activities of daily living. Cognition will be measured by the ADAS-Cog-11 and activities of daily living will be measured by the ADCS-ADL. Secondary efficacy measures: An additional measure of cognition will be the ADAS-Cog-13. Global assessment of change will be measured by the CIBIC+. Neuropsychiatric symptoms and psychopathology will be measured by the NPI. Subject dependency will be measured by the DS. Tertiary efficacy measures: Healthcare resource utilization, and quality of life will be assessed by the RUD Lite, and the EQ-5D. Pharmacokinetic evaluation: Plasma levels of RVT-101 and donepezil will be measured, and standard population PK parameters will be calculated for RVT-101. Safety evaluation: Safety will be based on adverse events (AEs), changes in physical examinations, vital signs, electrocardiograms

	(ECGs), suicidality (via the Columbia Suicide Severity Rating Scale [C-SSRS]) and routine clinical laboratory assessments.
Statistical Methods	Efficacy: Treatment comparisons between the RVT-101 and placebo groups in ADAS-Cog-11 and ADCS-ADL scores change from baseline at Week 24 will be analyzed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation. Additional analyses for the change from baseline at Week 24 endpoints including ADAS-Cog-13, CIBIC+, NPI, and DS will be analyzed using the same method as that for the primary endpoints. The CIBIC+ will also be analyzed using the Cochran-Mantel-Haenszel test. Treatment comparisons between the RVT-101 and placebo groups for the responder endpoints will be analyzed using logistic regression and compared using the Cochran–Mantel–Haenszel test. The RUD Lite, and the EQ-5D will be summarized descriptively by treatment. Treatment comparisons between RVT-101 and placebo will be analyzed using an analysis of covariance (ANCOVA) model. Pharmacokinetic: Plasma concentrations for RVT-101 and donepezil will be measured. RVT-101 PK parameters (area under the concentration-time curve at steady state [AUC_{tss}], peak concentration at steady state [$C_{max\text{-}ss}$], and minimum (trough) concentration at steady state [$C_{min\text{-}ss}$]) for each subject will be estimated via a population PK model using nonlinear mixed effect analysis. Safety: Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, physical examination, C-SSRS, and ECG parameters.

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 (AChEI). AChEIs increase levels of acetylcholine (ACh), 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 AChEI, 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 AChEIs 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 AChEI starts to wane, and there are no treatments currently approved for adjunct therapy to AChEIs 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 AChEIs (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 AChEIs (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 ADSC-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 effects of RVT-101 on cognition and activities of daily living observed in the AZ3110866 study provide a strong rationale for the continued development of RVT-101 as an adjunctive therapy to donepezil for the treatment of patients with AD. This Phase 3 study seeks to confirm the previous study results that demonstrated a treatment effect of RVT-101 on both cognition and activities of daily living when added to stable donepezil treatment when compared to treatment with donepezil alone. This study will also provide further information on the safety and tolerability of the 35-mg dose of RVT-101 when used in combination with donepezil. The primary objective of this study is to assess the effects of a 35-mg dose of RVT-101 compared with placebo when added to stable treatment with donepezil on the co-primary endpoints of cognition as measured by ADAS-Cog 11 item subscale (ADAS-Cog-11; Rosen et al, 1984) and activities of daily living as measured by ADCS-ADL (Galasko et al, 1997) after 24 weeks of double-blind treatment. The ADAS-Cog is a widely recognized scale for the assessment of cognition in clinical trials with subjects with AD, and the ADCS-ADL is similarly widely used for the assessment of function and activities of daily living. Both scales have established psychometric properties and have been employed in previous AD studies, supporting their inclusion as primary endpoints in this study.

3.3. Dose Rationale

A daily dose of 35 mg RVT-101 was selected for use in this study based on the results of the AZ3110866 study. This dose, administered in addition to donepezil, was shown to be well tolerated and when added to stable donepezil treatment 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.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on cognitive function as measured by the ADAS-Cog-11 after 24 weeks of treatment	ADAS-Cog-11 score change from baseline to Week 24
To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on activities of daily living as measured by ADCS-ADL scale after 24 weeks of treatment	ADCS-ADL score change from baseline to Week 24
Secondary	
To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on cognition as measured by the ADAS-Cog-13 (ADAS-Cog-11 plus delayed recall and total digit cancellation) after 24 weeks of treatment	ADAS-Cog-13 score change from baseline to Week 24
To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on global clinical assessment of change as measured by CIBIC+ after 24 weeks of treatment	CIBIC+ score at Week 24
To assess how baseline MMSE score affects efficacy outcome measures after 24 weeks of treatment	ADAS-Cog score change from baseline; ADCS-ADL score change from baseline; CIBIC+ score; all assessed by MMSE baseline score
To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory (NPI) after 24 weeks of treatment	NPI score change from baseline to Week 24
To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on an analysis of responders based on prespecified efficacy evaluations	Analysis of responders defined as improvement of at least 3 points on ADAS-Cog-11 from baseline AND at least no worsening on ADCS-ADL from baseline AND no worsening on CIBIC+ at 24 weeks

To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on subject dependency as measured by the Dependence Scale (DS)	DS score change from baseline to Week 24
To measure RVT-101 plasma concentrations and donepezil plasma concentrations in study subjects	Measurement of concentrations of RVT-101 and donepezil in plasma
To estimate the PK parameters of RVT-101 and explore relationships to efficacy or safety endpoints, as appropriate	Steady state area under the concentration-time curve ($AUC_{\tau ss}$), peak concentration ($C_{max\text{-}ss}$), and minimum concentration ($C_{min\text{-}ss}$) of RVT-101 in plasma
To assess the safety and tolerability of RVT-101 as an adjunct therapy to stable donepezil treatment	Occurrence of adverse events (AEs) and changes in physical examinations, vital signs measurements, electrocardiograms (ECGs), routine laboratory assessments, and Columbia Suicide Severity Rating Scale (C-SSRS)
Tertiary	
To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on healthcare utilization as measured by the Resource Utilization in Dementia Lite (RUD Lite)	RUD Lite score change from baseline to Week 24
To assess the effects of RVT-101 versus placebo as adjuncts to stable donepezil therapy on quality of life as measured by the EuroQOL 5 dimensions questionnaire (EQ-5D)	EQ-5D score change from baseline to Week 24

5. STUDY DESIGN

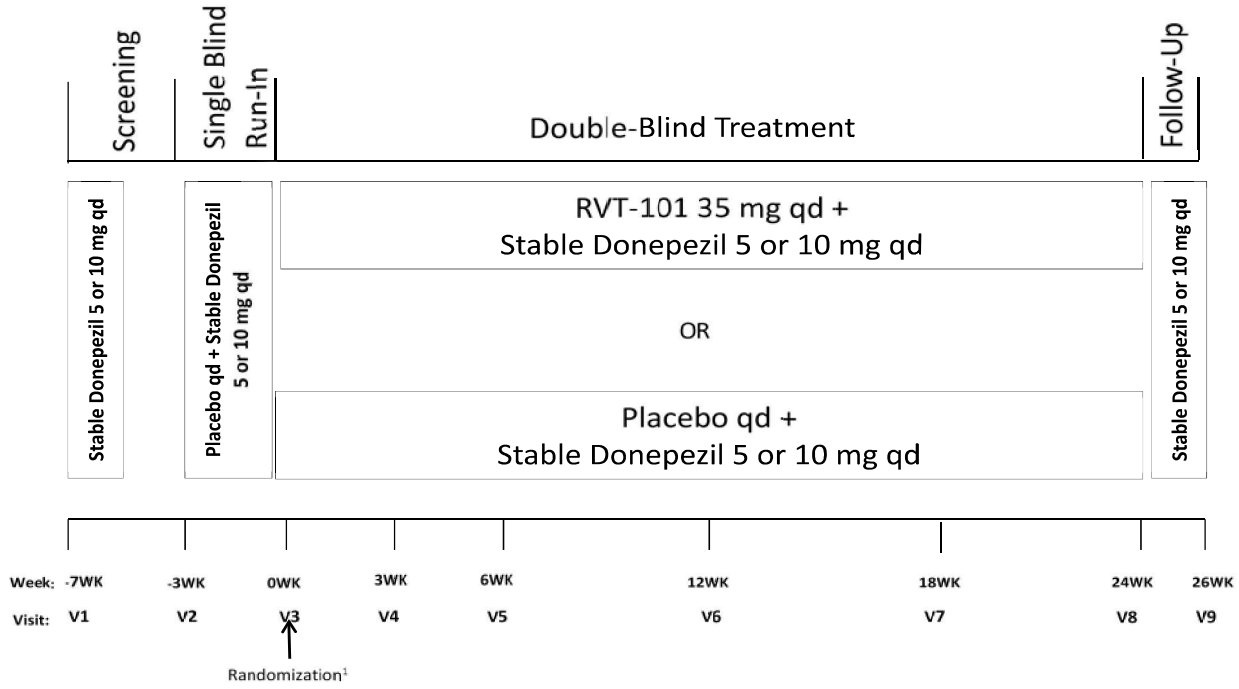
5.1. Overall Design

This is a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in patients with mild to moderate AD who are on stable donepezil therapy. The efficacy and safety of RVT-101 at a dose of 35 mg will be evaluated over a 24-week treatment period. Approximately 1150 subjects will be enrolled. The randomization ratio will be 1:1 (RVT-101:placebo) and will be stratified by baseline MMSE score. The primary endpoints will be measured after 24 weeks of treatment. Study participation will last approximately 33 weeks: 0 to 4 weeks for Screening, a 3-week Single-Blind Run-In Period to evaluate baseline status, a 24-week randomized Double-Blind Treatment Period, and a 2-week Follow-Up Period (for subjects who do not enter the open-label extension study RVT-101-3002).

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. If a greater than 3 point difference between the Screening and Baseline MMSE score is in the opinion of the investigator due to recent changes in AD medication, the Run-In period may be extended for an additional 3 weeks after discussion with the Medical Monitor, during which time MMSE stability defined as less than or equal to 3 point change over 3 weeks must be observed.

6. SUBJECT POPULATION

6.1. Type and Number of Subjects

Approximately 1150 subjects with mild to moderate AD who are on stable donepezil therapy will be enrolled.

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

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 AD in accordance with the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for AD (McKhann et al, 2011).
2. Subject has a documented history of at least 4 months of ongoing donepezil therapy for AD, with stable dosing of 5 or 10 mg/day for at least the last 2 months and with no intent to change for the duration of the study.
3. Subject has an MMSE score 12 to 24 inclusive at Screening and a Baseline MMSE score 10 to 26 inclusive. The difference between the Screening and Baseline MMSE score is less than or equal to 3 points. If a greater than 3-point difference between the Screening and Baseline MMSE score is in the opinion of the investigator due to recent changes in AD medication, the Run-In period may be extended for an additional 3 weeks after discussion with the Medical Monitor, during which time MMSE stability, defined as less than or equal to 3-point change over 3 weeks, must be observed.
4. Subject has a Hachinski Ischaemia score less than or equal to 4 at Screening.
5. Magnetic resonance imaging (MRI) or computed tomography (CT) scan performed within 12 months before screening with findings consistent with the diagnosis of dementia due to AD without any other clinically significant pathologies. If an MRI (preferred) or CT scan is unavailable or was performed longer than 12 months prior to Screening, one must be performed during the Screening Period (prior to Run-In).
6. Age greater than or equal to 50 years to less than or equal to 85 years at the time of Screening.
7. If female, subject 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 adequate methods of birth control. Female subjects for whom menopausal status is in doubt in the opinion of the investigator will be required to use an adequate form of birth control. Acceptable, adequate form of birth control is defined as consistent use of combined effective methods of contraception including at least 1 barrier method.

Male subjects who are sexually active will also be required to use an adequate form of birth control as described above.

8. Subject has the ability to comply with procedures for cognitive and other testing in the opinion of the investigator.
9. Subject must be able to ingest pills (in tablet form) whole.
10. Subject lives with (or has substantial periods of contact with) a regular caregiver who is willing to attend visits, oversee the subject's compliance with protocol-specified procedures and study medication, and report on subject's status, and who has substantial contact with the subject. If the caregiver does not cohabitate with the subject, he/she ideally should have a minimum of 10 hours total and at least 3 days contact with the subject per week. Prior to randomization, study representatives will review eligibility of non-cohabitating caregivers. Every effort should be made to have the same caregiver throughout the study.
11. 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.
12. Caregiver has provided full written informed consent on his/her own behalf prior to the performance of any protocol-specified procedure.
13. General health status is acceptable for participation in a 24-week 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. Diagnosis of possible, probable, or definite vascular dementia in accordance with National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche l'Enseignement en Neurosciences criteria.
2. History and/or evidence (including CT or MRI scan performed within the past 12 months or at Screening) 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; or Parkinson's disease.

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. Focal findings on the neurological exam (excluding changes attributable to peripheral injury) that are inconsistent with a primary diagnosis of AD.
5. History of existing negative amyloid positron emission tomography scan or similar brain amyloid imaging, or Screen Failure from research trial due to negative amyloid imaging within 5 years. Note: amyloid scan is not required for participation in this study.
6. 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 including, but not limited to, frontotemporal dementia, Lewy body dementia, or others.

Confounding Medical Conditions

7. 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.
8. Significant suicide risk as defined by (1) suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year, at Screening or at Baseline, or; (2) suicidal behaviors within the past year, or; (3) clinical assessment of significant suicidal risk during subject interview.
9. Current psychosis that in the opinion of the investigator would interfere with the subject's ability to participate in this study.
10. 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.
11. 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.
12. 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.
13. 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.
14. History of Down syndrome or Intellectual Development Disorder.

Concomitant Medications

15. Participation in another investigational drug or device study in AD during the 60 days prior to the Screening Visit (Visit 1), or within 5 half-lives of use of the investigational drug prior

to the Screening Visit, whichever is longer. In addition, subjects who were previously screened for another study in AD 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. However, Screen Failures due to negative amyloid imaging within 5 years will not be eligible for enrollment (see exclusion criterion 5).

16. Treatment with any concomitant medications as detailed in Table 1. Memantine and other treatments for dementia including AChEIs other than donepezil must have been discontinued 30 days prior to entry into the Single-Blind Run-In Period. Other 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. Subjects taking memantine or other agents to treat cognitive impairment associated with AD at the time of Screening will be considered Screen Failures. However, subjects with recent discontinuation prior to Screening of memantine or other agents to treat cognitive impairment who will have been discontinued for 30 days prior to the Single-Blind Run-In Period may continue. Subjects who screen fail may be rescreened once (see Section 6.5).

Unacceptable Test/Laboratory Values

17. Postural hypotension (fall in systolic blood pressure of greater than 30 mmHg or fall in diastolic blood pressure of greater than 20 mmHg on standing compared to sitting) at the time of screening. Subjects who present at the time of screening with postural hypotension yet have no known history of postural hypotension, nor underlying medical condition related to hypotension, may be rescreened.
18. Persistent or recurrent liver enzyme elevations, alanine transaminase (ALT) and/or aspartate aminotransferase (AST) greater than or equal to 2.0 times upper limit of normal (ULN).
19. Total bilirubin over 1.5 x ULN except due to documented Gilbert's disease.
20. Calculated creatinine clearance less than 40 mL/min (Cockroft-Gault formula) at Screening:

    Adult males: $[(140 - \text{age in years}) \times (\text{weight in kg})] \div 72 \times \text{serum creatinine}^*$

    Adult females: $0.85 \times [((140 - \text{age in years}) \times (\text{weight in kg})) \div 72 \times \text{serum creatinine}^*]$

    * in mg/dL
21. Positive hepatitis B surface antigen or hepatitis C antibody test.
22. 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. 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.

Other

23. Previous exposure to RVT-101 or SB742457.
24. Subject is unable to take study medication 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 medication or procedures.
25. 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.
26. Subject was prescribed cognitive tasks for cognitive rehabilitation performed under medical supervision in the 3 months prior to Screening or plans to participate in cognitive rehabilitation during the study.
27. Subject has participated in a program of neurostimulation in the past 3 months or plans to participate in a program of neurostimulation during the course of the study.

6.4. Other Eligibility Criteria Considerations

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

- RVT-101 Investigator's Brochure
- Package insert/label for donepezil hydrochloride.

6.5. Screening Failures

Screen Failures are defined as subjects who sign an informed consent form (ICF) for RVT-101-3001 but are never subsequently randomized and who do not enter the Single-Blind Run-In Phase. A minimal set of screen failure information is required including demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Subjects who are Screen Failures may be rescreened once only after approval by the study Medical Monitor.

6.6. Withdrawal Criteria

6.6.1. Reasons for Withdrawal

A withdrawal from the study is defined as withdrawing any time after entering the Single-Blind Run-In Phase and before completion of the Week 24 Visit (Visit 8). Subjects who permanently discontinue use of investigational product will be considered to be withdrawn from the study. Subjects may withdraw from the study at any time and for any reason. The investigator (or designee) must document the reason for withdrawal in the appropriate section of the electronic case report form (eCRF). Information related to AEs will continue to be collected as per usual

procedures on subjects who have discontinued 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. Subjects may discontinue from treatment with study investigational product but may agree to continue to be followed for additional safety evaluation.

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 study medication between scheduled clinic visits, he/she should be recalled to the clinic as soon as possible and preferably within 7 days of stopping study medication for the Early Termination Visit.

Lost to follow-up: If a subject is lost to follow-up, every effort must be made by study center personnel to contact the subject, inquire about the reason for discontinuation/withdrawal, and follow up with any unresolved AEs/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 its matching placebo, and will be provided by Axovant Sciences. RVT-101 and placebo tablets will be indistinguishable from each other.

Investigational product for the Single-Blind Run-In Period (Weeks -3 to 0) will be supplied as single individual bottles, each bottle containing 50 tablets which is sufficient medication for 3 weeks plus 29 days overage. Investigational product for the Double-Blind Treatment Period (Weeks 0 to 24) will be supplied at Visits 3, 5, 6, and 7 as a single individual bottle containing 50 tablets, which is sufficient for 6 weeks plus 8 days overage. A new bottle of investigational product will be dispensed at each visit *except* at Visit 4, where no drug is dispensed. In the event that the Single-Blind Run-In period is extended to repeat the MMSE, no new investigational product will be dispensed. Drug accountability will be checked, and subjects will be redispensed the study medication bottles they received at Visit 2.

Subjects enrolled in this study will have been on donepezil for at least 4 months and on a stable dose of 5 or 10 mg/day for at least 2 months prior to enrollment and will continue this regimen unchanged for the duration of the study. Axovant Sciences will supply donepezil tablets in this study at the stable clinical dose for each subject. Study-dispensed donepezil will start in the Single-Blind Run-In Period. Subjects should be clearly instructed to take only study-dispensed donepezil during the duration of this study until V8, and to discontinue their clinical supply of donepezil provided by their personal physician. Subjects should be instructed to take their study-supplied donepezil exactly as they had been taking their clinically prescribed donepezil during the previous 2 months, including at the same time of day. Compliance with study-dispensed donepezil should be assessed at each visit. Confirmation of discontinuation of clinically supplied donepezil from subject and caregiver should be obtained at Visit 4 (Week 3) and re-confirmed thereafter as needed. Subjects will need to re-start their clinical supply of donepezil (clinically prescribed by the Investigator or treating physician) after V8; subjects not entering the open-label extension study RVT-101-3002 will remain at the same stable dose until V9.

Study-supplied donepezil will be supplied throughout the study as single individual bottles that contain 90 tablets. This is sufficient to cover all visit intervals plus windows as allowed by the protocol. A new bottle of donepezil will be dispensed according to the Time and Events Schedule in Table 2. In the event that the Single-Blind Run-In period is extended to repeat the MMSE subjects will be redispensed the medication they received at Visit 2.

Characteristic	Investigational Product	
Product name:	RVT-101	Placebo
Formulation description:	Pink film-coated round tablets	Pink film-coated round tablets
Dosage form:	35-mg tablet	Placebo tablet
Unit dose strength(s)/ Dosage level(s):	35 mg (1 tablet per dose)	N/A (1 tablet per dose)
Route of administration:	Oral	Oral
Duration (Run-in Period):	N/A	3 weeks
Duration (Treatment Period):	24 weeks	24 weeks
Dosing instructions:	Take 1 tablet orally each morning without regard to food	Take 1 tablet orally each morning without regard to food
Clinical Supplier	Catalent Pharma Solutions, Kansas City, MO USA	Catalent Pharma Solutions, Kansas City, MO USA

Characteristic	Study-Dispensed Donepezil
Product name:	Donepezil hydrochloride (5 mg and 10 mg tablets)
Formulation description:	5 mg tablets: white to off white film-coated, round tablets debossed with ML89 on one side 10 mg tablets: yellow film-coated round tablets debossed with ML88 on one side
Dosage form:	Tablet
Unit dose strength(s)/ Dosage level(s):	5 mg (1 tablet per dose) and 10 mg (1 tablet per dose)
Route of administration:	Oral
Duration (Run-in Period):	3 weeks
Duration (Treatment Period):	24 weeks
Dosing instructions:	Take 1 tablet orally as prescribed
Clinical Supplier	Catalent Pharma Solutions, Kansas City, MO USA

7.2. Randomization/Treatment Assignment

Subjects will be assigned to receive RVT-101 or placebo as adjunct therapy to existing stable donepezil therapy in accordance with the randomization schedule, prior to the start of the Double-Blind Treatment Period, using validated software.

Following confirmation of eligibility at Visit 3 (end of Single-Blind Run-In Period), subjects will be randomized to placebo or RVT-101 in a 1:1 ratio. Randomization will be stratified according to subjects' baseline MMSE scores, so as not to exceed the limits described in Section 10.2.

7.3. Blinding

This will be a double-blind study. The study will include a 3-week Single-Blind Run-In Period during which investigators will know that the subject is taking placebo but the subject and caregiver will not. This will be followed by a 24-week Double-Blind Treatment Period when neither subjects nor their caregivers nor investigators will know which of the 2 treatments the subject is receiving. Subjects will be informed that they will receive placebo at some point during the study but they will not know when this will be. Subjects will not be informed of transition from the Single-Blind Run-In Period to the Double-Blind Treatment Period. RVT-101 and placebo will be provided as tablets that are indistinguishable in appearance, smell, and taste. Donepezil will be supplied at the start of the Run-In Period and will be clearly marked throughout the study in an unblinded fashion.

The following will apply:

- The investigator or treating physician may unblind a subject's treatment assignment. Such a measure should be taken **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the 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 contact the Medical Monitor to discuss the potential need for unblinding. Unblinding will be done through the interactive voice response system (IVRS)/interactive web response system (IWRS). The procedure of unblinding for a specific subject is provided in the Study Reference Manual.
- If, for safety reasons, the investigator determines that the subject's treatment must be immediately unblinded to provide adequate medical treatment, the investigator must inform the Medical Monitor about the unblinding as soon as possible, but without revealing the treatment assignment of the unblinded subject.
- The sponsor will be informed without delay of the decision to unblind any subject and will determine whether any additional measures need to be taken for the safety of subjects currently in the study.
- Any other requests to reveal a subject's treatment identity must be requested of, and approved by, Axovant Sciences.

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

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

7.4. Packaging and Labeling

RVT-101 35-mg tablets and matching placebo tablets will be packaged in high-density polyethylene bottles. Labels for RVT-101 and placebo bottles will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

A sample of the information included in the label for investigational product is provided in Figure 2 and for study-supplied donepezil in Figure 3 (5 mg tablets) and Figure 4 (10 mg tablets).

Figure 2 RVT-101 35 mg or placebo

Protocol RVT-101-3001 Subject Number:

Lot number: #####/#####

Bottle ID No: xxxxx

Contains RVT-101 35 mg tablets or Placebo tablets

Quantity: 50 Tablets/Bottle

Dosing Directions: Take one tablet orally each morning with or without food. Do not cut or crush.

Store at room temperature (59-86°F; 15-30°C). Protect from light.

Caution: New Drug—Limited by Federal law to investigational use.
Keep out of reach of children.

Sponsor: Axovant Sciences Ltd.
Phone # +1 (646) 495-8197

Figure 3 Donepezil Hydrochloride 5 mg

Protocol RVT-101-3001 Subject Number:
Lot number: #####
Bottle ID No: xxxxx Expiry date: MMMYYYY

Contains: Donepezil Hydrochloride 5 mg

Quantity: 90 Tablets/Bottle

Dosing Directions: Take one tablet orally as prescribed.

Store at room temperature (59-86°F; 15-30°C). Protect from light.

For Clinical Trial Use only. Keep out of reach of children.

Sponsor: Axovant Sciences Ltd.
Phone # +1 (646) 495-8197

Figure 4 Donepezil Hydrochloride 10 mg

Protocol RVT-101-3001 Subject Number:
Lot number: #####
Bottle ID No: xxxxx Expiry date: MMMYYYY

Contains: Donepezil Hydrochloride 10 mg

Quantity: 90 Tablets/Bottle

Dosing Directions: Take one tablet orally as prescribed.

Store at room temperature (59-86°F; 15-30°C). Protect from light.

For Clinical Trial Use only. Keep out of reach of children.

Sponsor: Axovant Sciences Ltd.
Phone # +1 (646) 495-8197

7.5. Preparation/Handling/Storage/Accountability

No special preparation of investigational product is required. Investigational product will be stored at up to 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 both investigational product and study-supplied donepezil for each bottle dispensed.
- Further guidance and information for final disposition of unused investigational product 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 study monitor, Medical Monitor, and/or the Axovant Sciences study contact.
- A Material Safety Data Sheet/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from Axovant Sciences.

7.6. Compliance with Investigational Product and Study-Supplied Donepezil Administration

When subjects are dosed at the site, they will receive investigational product 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 investigational product and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the investigational product.

Every effort should be made to encourage subject compliance with the dosage regimen as per protocol for both investigational product and continued treatment with study-supplied donepezil. The investigator is responsible for discussing methods to ensure high treatment compliance with subjects and caregivers before randomization. All subjects and their caregivers should be instructed to return medication 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 eCRF. 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 blinded investigational product or donepezil for a period exceeding 7 consecutive days. While interruptions in investigational product administration should be avoided wherever possible, short-term interruptions (less than or equal to 7 days) 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.

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.
- Obtain a plasma sample for PK analysis within 2 days of the overdose of investigational product, if requested by the Medical Monitor (determined on a case-by-case basis), and
- Document the quantity of the excess dose as well as the time of administration of the overdose in the eCRF.

It is not necessarily required that the investigator unblind a subject who has taken an overdose. As noted in Section 7.3, unblinding should only be done in the case of an emergency OR in the event of a serious medical condition when knowledge of the investigational product is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator.

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

7.8. Treatment after the End of the Study

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

After completion of Visit 8, the subject may be considered for enrollment in the open-label extension study RVT-101-3002. Only subjects who do not enroll in the extension study will complete the Follow-up Visit (Visit 9).

7.9. Concomitant Medications and Non-Drug Therapies

7.9.1. Permitted Medications and Non-Drug Therapies

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

7.9.2. Prohibited Medications and Non-Drug Therapies

Subjects who begin treatment during the study with any prohibited medication, or begin cognitive tasks for cognitive rehabilitation performed under medical supervision or neurostimulation should be withdrawn from the study. However, where such treatment has been for less than or equal to 7 days, termination of the prohibited medication or treatment and continuation in the study may be considered by the investigator in discussion with the Medical Monitor, based on subject safety and the perceived need for the prohibited treatment. If treatment with a conditional medication is initiated during the study and will be prescribed chronically, the investigator should discuss this with the Medical Monitor before determining whether to continue the subject in the study. Use of prohibited and conditional medications and treatments must be documented in the Concomitant Medications section of the eCRF. Prohibited and conditional medications are listed in Table 1.

Table 1. List of Prohibited and Conditional Medications

Prohibited Medications: Not allowed during the study or within 5 half-lives prior to Screening	Prohibited Medications: Not allowed during the study or within 30 days prior to Single-Blind Run-In Period	Conditional Medications: Not allowed unless prescribed at a stable dose for at least 2 months prior to Screening; dose during the study should be stable, if possible
• 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 Pgp inhibitors[3] (itraconazole, ketoconazole, cyclosporin, diltiazem, verapamil, quinidine, and carvedilol)	• Acetylcholinesterase inhibitors other than donepezil (i.e., galantamine, rivastigmine, tacrine) • Memantine • Axona® (caprylidene)	• Antidepressants (other than MAO inhibitors) • Thyroid hormones • Atypical antipsychotics (e.g., risperidone) • Benzodiazepines and other sedatives/hypnotics Note: Benzodiazepines or other sedatives/hypnotics (including antihistamines) with half-life less than 6 hours can be taken on an as-needed basis but must not be taken within 5 half-lives prior to cognitive testing.

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

7.10. Lifestyle and/or Dietary Restrictions

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. All study assessments should be conducted by the investigator, and/or a suitably qualified designee approved and documented for this study. All raters will be trained and certified to perform the specific rating scales in this study.

For Visit 2 there is a visit window of + 5 days. In the event the Single-Blind Run-In period is extended to repeat the MMSE, the new Visit 2 window will be + 3 days. For Visits 4 and 5 there is a visit window of ± 3 days; for all other post-randomization visits, there is a visit window of ± 5 days. It is important that all visits should be scheduled relative to the baseline visit, except for Visit 9 which should be scheduled relative to the last dose of IP. If the visit window is used, the subsequent visit should remain according to the planned visit schedule (i.e., the subsequent visit date should not be re-calculated from the date of the previous visit but should remain relative to baseline).

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

Every effort should be made to administer the ADAS-Cog within ±1 hour of the time of day of the baseline administration on subsequent visits for each subject due to the potential for circadian fluctuation in scores.

The order of rating scales should, when possible, be held constant, with the ADAS-Cog given to the subject first at each visit. The ADCS-ADL should be the first rating scale given to caregivers when possible at each visit.

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

- 12-lead ECG
- Vital signs
- Blood draws

Screening Period (up to 28 days before Visit 2): Subjects will be screened for eligibility during the Screening Period. Subjects who do not qualify for the study during this period will be considered Screen Failures. An ICF will be signed by each subject, if he or she is able, or by the caregiver with subject assent. An ICF will also be signed by the caregiver before any study-specific procedures are performed. Subjects will be screened according to study inclusion/exclusion criteria. This Screening Period may be extended for up to an additional

14 days if needed to complete assessment activities after approval by the study Medical Monitor. Subjects who are Screen Failures during the Screening Period may be rescreened after discussion with the Medical Monitor. Note: Subjects who are Screen Failures may be rescreened only once.

Single-Blind Run-In Period (21 + 5 days before Visit 3): At Visit 2, subjects who meet all study screening criteria will enter a Single-Blind Run-In Period. Investigational product will be dispensed. Subjects will be instructed to take the investigational product once daily in the morning. Subjects will be instructed to take the first Single-Blind Run-In investigational product (single-blind placebo) during the study visit. Study-supplied donepezil matching the subject's stable clinical dose will also be dispensed. Subjects and caregivers should be instructed that subjects are to take study-supplied donepezil throughout the course of the study and to discontinue any clinically dispensed donepezil prescribed by subjects' personal physician. Visit 2 assessments will be performed according to Table 2 below. To qualify for randomization at Baseline (Visit 3) subjects must return unused study medication, be considered capable of completing study assessments, remain within study-specified criteria for MMSE, and meet all other eligibility requirements.

The Single-Blind Run-In Period may be extended for 3 weeks after discussion with the Medical Monitor for subjects who do not meet MMSE stability criterion for randomization in the event that the change in MMSE is seen in the setting of recent change in AD therapy. Subjects who require this run-in extension period will have a new baseline visit window of no more than 21 to 24 days after the originally intended baseline. This subsequent visit will then serve as the subject's baseline if randomization criteria are met. No new investigational product or study-supplied donepezil will be dispensed for the additional run-in period; subjects should be instructed to continue taking blinded investigational product and study-supplied donepezil dispensed at Visit 2.

The ADAS-Cog assessment should be the first assessment performed, followed by the MMSE. If the MMSE score does not meet the stability criterion for randomization, no other assessments should be performed. If after discussion with the Medical Monitor it is determined that the Single-Blind Run-In Period may be extended by 3 weeks per the criterion above, the subject should be scheduled to return to the clinic in 3 weeks' time (+ 3 days), and all baseline assessments should be performed at this repeat visit.

Baseline (Visit 3) and Double-blind Treatment (Visit 4 through Visit 8): At Visit 3 (Baseline), prior to ingestion of double-blind investigational product, Baseline assessments will be performed to determine subject eligibility. Eligible subjects will be randomized to 1 of 2 groups, RVT-101 or placebo, for the 24 weeks of double-blind treatment assessment. Double-blind investigational product and study-supplied donepezil will be dispensed at Visits 3, 5, 6, and 7. At the Baseline visit, subjects will ingest the first dose of investigational product in the clinic in the presence of study center personnel; this may cause dosing to not occur in the morning on this visit according to the timing of the subject's visit schedule. All additional doses will be ingested as outpatients, except for the Visit 6 dose, which should occur in the clinic after the PK sample collection. At each visit, subjects will be reminded to take 1 tablet of blinded investigational product each morning, and to take study-provided donepezil in accordance with

their previously prescribed treatment regimen. Discontinuation of donepezil prescribed by subjects' personal physician should be confirmed at Visit 3 (Baseline + 5 days). As needed, subjects should be reminded to maintain discontinuation of clinically prescribed donepezil while taking study-supplied donepezil. Note: no investigational product or study-supplied donepezil will be dispensed at Visit 4 (Week 3); subjects will be redispensed the medication that they received at Visit 3 after drug accountability has been performed. Compliance with investigational product and study-supplied donepezil should be assessed at Visit 4, and study bottles returned to subjects to continue until Visit 5 (Day 42 ± 3 days) when the next bottles will be dispensed.

Throughout the Baseline and Double-Blind Treatment Periods, all clinic visits will be scheduled according to specified visit windows, and all specified assessments will be completed (Table 2). The administration of the ADAS-Cog should be kept within a ± 1-hour window of the time of day of the Baseline assessment for each subject to diminish the potential impact of circadian fluctuations in cognition. This should be taken into consideration when scheduling and performing baseline ADAS-Cog assessments.

The order of assessments should remain consistent during the Double-Blind Treatment Period, and when possible, the ADAS-Cog should be given to the subject first, followed by the other efficacy endpoint scales. If possible, other assessments, including ECG, vital signs, and blood draws, should be performed after cognitive testing and other endpoint scales. When possible ADCS-ADL should be given as the first assessment to the caregiver followed by other endpoint scales.

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

Subjects who prematurely discontinue double-blind investigational product should be encouraged to return to the clinic for an Early Termination Visit, and the early termination procedures should be performed as indicated in the time and events schedule.

Safety Follow-Up: All subjects who complete the Double-Blind Treatment Period and do not enter the open-label extension study RVT-101-3002 will be required to attend a Safety Follow-Up clinic visit (Visit 9) 14 to 19 days after the last day of treatment.

Table 2. Time and Events Schedule

Study Period:	Screening	Run-in	Baseline	Treatment					Follow-up[11]	ET
Study Visit Number:	V1	V2	V3[1]	V4	V5	V6	V7	V8	V9	ET
Study Week:	W(-7)	W(-3)	W0	W3	W6	W12	W18	W24	W26	
Study Day: relative to Baseline unless specified	Up to 28 days before V2	21 + 5 days[1,2] before V3	0	21 ± 3	42 ± 3	84 ± 5	126 ± 5	168 ± 5	14 to 19 days after last dose of IP	
Informed consent	X									
Inclusion and exclusion criteria	X		X							
Demography	X									
Medical history	X									
Concomitant medications review	X	X	X	X	X	X	X	X	X	X
Urine drug screen	X									
C-SSRS	X		X	X	X	X	X	X	X	X
Randomization			X							
Dispense investigational product[3]		X	X		X	X	X			
Dispense study-supplied donepezil[3]		X	X		X	X	X			
Assess investigational product and study-supplied donepezil compliance			X	X	X	X	X	X		X
Physical exam/ current medical conditions [4]	X	X	X	X	X	X	X	X	X	X
Complete neurological exam	X		X			X			X	
MRI or CT [5]	X									
12-lead ECG	X	X	X	X	X	X	X	X	X	X
Vital signs [6]	X	X	X	X	X	X	X	X	X	X
Review adverse events		X	X	X	X	X	X	X	X	X
Serum OR urine pregnancy test [7]	X								X	X
Hep B, and Hep C screen [8]	X									
TSH, vitamin B_{12}, syphilis serology [9]	X									
Serum chemistry	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X
Blood alcohol content	X	X	X	X	X	X	X	X		
RVT-101 level [10]					X	X	X	X		
Donepezil level [10]			X			X		X		

Study Period:	Screening	Run-in	Baseline	Treatment					Follow-up[11]	ET
Study Visit Number:	V1	V2	V3[1]	V4	V5	V6	V7	V8	V9	ET
Study Week:	W(-7)	W(-3)	W0	W3	W6	W12	W18	W24	W26	
Study Day: relative to Baseline unless specified	Up to 28 days before V2	21 + 5 days[1,2] before V3	0	21 ± 3	42 ± 3	84 ± 5	126 ± 5	168 ± 5	14 to 19 days after last dose of IP	
Hachinski Ischaemia Scale	X									
ADAS-Cog		X	X	X	X	X	X	X		
MMSE	X		X							
ADCS-ADL		X	X	X	X	X	X	X		
CIBIS			X							
CIBIC+						X	X	X		
NPI			X			X	X	X		
DS			X					X		
RUD Lite			X					X		
EQ-5D			X					X		

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale – cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study Group – Activities of Daily Living Inventory; CIBIC+ = Clinician's Interview-Based Impression of Change Plus caregiver Interview; CIBIS = Clinician's Interview-Based Impression of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; CT = computed tomography; DS = Dependence Scale; ECG = electrocardiogram; ET = early termination; EQ-5D = EuroQOL 5 dimensions questionnaire; Hep = hepatitis; MMSE = mini-mental state examination; MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory; RUD Lite = Resource Utilization in Dementia Lite; TSH = thyroid stimulating hormone; V = visit; W = week.

Notes:

1. The Single-Blind Run-In Period may be extended for 3 weeks after discussion with the Medical Monitor for subjects who do not meet MMSE stability criterion for randomization in the event that the change in MMSE is seen in the setting of recent change in AD therapy. Subjects requiring this run-in extension period will have a new baseline visit window of no more than 21 to 24 days after the originally intended baseline. This subsequent visit will then serve as the subject's baseline if randomization criteria are met. No new study drug or study-supply donepezil will be dispensed for the additional run-in period; subjects should be instructed to continue taking blinded investigational product and study supply donepezil dispensed at Visit 2.
2. The ADAS-Cog assessment will be the first assessment performed, followed by the MMSE. If the MMSE score does not meet the stability criterion for randomization, no other assessments should be performed. If after discussion with the Medical Monitor it is determined that the Single-Blind Run-In Period may be extended by 3 weeks per the criterion above, the subject should be scheduled to return to the clinic in 3 weeks' time, and all baseline assessments should be performed at this repeat visit (refer to footnote 1).
3. No new drug will be dispensed at V4. The bottles and pill count should be checked for compliance at V4 , but no new medication will be dispensed at that visit.
4. Physical examinations at Screening and V8 will be full examinations; at all other study visits, an abbreviated physical examination is required.
5. MRI or CT scan will be performed between V1 and V2 if no scan has been performed within the previous 12 months. These scan findings must be consistent with the diagnosis of dementia due to AD without any other clinically significant pathologies.
6. Vital signs will include systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature, and body weight at each visit and height at screening. Postural changes in blood pressure will be assessed at screening.
7. Required only for women of child bearing potential.
8. 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.
9. 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.
10. All PK blood samples should be taken after cognitive testing, ECG, and vital signs measurements have been performed except for the Week 12 (V6) sample, which should be taken prior to dosing in the clinic.
11. Required only for subjects who do not enter the open-label extension study RVT-101-3002.

8.2. Critical Baseline Assessments

Those subjects whose MMSE at Baseline (Visit 3) has changed significantly (more than 3 points) from Screening (Visit 1) and/or those subjects whose MMSE at Baseline changes such that it falls outside the range 10-26 will not be randomized. The purpose of this is to exclude subjects whose baseline is so variable that any drug effect may not be clearly observable and also to exclude subjects whose baseline improves under placebo to the level of very mild, or whose baseline worsens to borderline severe, making effects of treatment intervention difficult to observe with the assessments included in this study. If a greater than 3-point difference between the Screening and Baseline MMSE score is in the setting of recent changes in AD medication, Single-Blind Run-In may be extended for an additional 3 weeks after discussion with the Medical Monitor, during which time MMSE stability defined as less than or equal to 3-point change over 3 weeks must be observed.

8.3. Study Assessments and Procedures

8.3.1. Efficacy Assessments

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

8.3.1.1. Mini-Mental State Examination (MMSE)

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

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

The 11-item and 13-item ADAS-Cog (Rosen et al, 1984; Mohs et al, 1997) assesses a range of cognitive abilities including memory, comprehension, orientation in time and place, and spontaneous speech. Most items are evaluated by tests, but some are dependent on clinician ratings on a 5-point scale. The ADAS-Cog-11 total score range is from 0 to 70, with a higher score indicating more severe cognitive impairment. The ADAS-Cog-13 is the ADAS-Cog-11 with 2 additional items: delayed word recall and total digit cancellation. Scores for the ADAS-Cog-13 range from 0 to 85 with higher scores indicating greater dysfunction. The scale takes approximately 30 to 40 minutes to administer. During the study visits where the ADAS-Cog is performed, the full ADAS-Cog-13 test items will be collected. The primary analysis will be of the ADAS-Cog-11 subset of tests from that battery and the full ADAS-Cog-13 will be analyzed as a secondary endpoint. When possible, the ADAS-Cog should always be the first assessment

conducted and should be administered, if possible, within ±1 hour of the time of baseline administration at all subsequent visits to control for potential impact of circadian variation in performance.

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

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

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

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

8.3.1.5. Neuropsychiatric Inventory (NPI)

The NPI (Cummings et al, 1994) is a behavior rating scale composed of a 12-item structured interview of the caregiver that is scored from 0 to 144 (the higher the score, the greater the psychiatric disturbance). It assesses 12 behavioral disturbances occurring in dementia patients: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor activity, night-time behavior disturbances, and eating disturbances. Both the frequency and the severity of each behavior are determined.

8.3.1.6. Resource Utilization in Dementia Lite (RUD Lite)

The RUD scale (Wimo et al, 1998) is designed to assess caregiver burden and provide pharmacoeconomic data related to AD. The RUD Lite 3.3 includes both baseline and follow-up questions. Caregiver-related questions include a description of the caregiver for demographic information and time spent caring for the subject and changes in work status. Subject-related questions include residential status and healthcare resource utilization. In the event that a subject changes caregiver during the course of the study, the new caregiver must complete a baseline questionnaire at the earliest possible visit.

8.3.1.7. Dependence Scale

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

8.3.1.8. 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 (Rabin and deCharro, 2001). 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 (EQ-VAS). The EQ-5D descriptive system includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-VAS records overall health status on a 20-cm vertical line with a score of 0 (worst health one can imagine) to 100 (best health one can imagine).

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.

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

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 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.

8.3.2.1.2. 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 contact. 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.

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.

Instructions for assessing causality are provided in the Study Reference Manual.

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 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, 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. In addition, the initial SAE report should include all pertinent known information about the SAE and the affected subject. In addition, the investigator should provide a narrative to describe the course of events including any treatments or relevant procedures. Follow-up information, which may include copies of relevant subject records and other documents not available at the initial SAE report must be sent to Worldwide Clinical Trials as soon as available. Follow-up SAE reports may describe the evolution of the reported event and any new assessment of outcome and/or relationship to investigational product. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant medical/hospital records, pathology, or autopsy reports.

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 (those not listed in the Investigator Brochure) according to local regulatory requirements and Axovant Sciences policy and are forwarded to investigators as necessary.

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

8.3.2.2. Safety Monitoring Committee

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-101-3001

on an ongoing basis. Members of the committee will include clinicians and a biostatistician who are experienced in the conduct and monitoring of clinical studies. No Axovant Sciences employee or investigator involved in the RVT-101-3001 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 and will contain blinded interim safety data. However, the SMC will be provided unblinded treatment codes for these studies if a significant safety concern is identified. Ad hoc SMC meetings may be held as necessary.

After reviewing the interim safety data from RVT-101-3001, 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.

8.3.2.3. Physical Examinations

Physical examinations will be performed as indicated in Table 2. A complete physical examination will include, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Neurological examinations will include assessment of gait, balance, coordination, cranial nerves and motor and sensory systems. A brief, symptoms-directed physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, and abdomen (liver and spleen). Physical examinations at Screening and Visit 8 will be full examinations; at all other study visits, an abbreviated physical examination is required.

8.3.2.4. Vital Signs

Vital signs will be measured after the subject has been in the seated position for 5 minutes and will include temperature, systolic and diastolic blood pressures, pulse rate, and respiratory rate. Postural changes will be measured within 3 minutes of appropriate body position change. Body weight will also be recorded at each visit and height will be recorded at Screening.

8.3.2.5. Electrocardiogram (ECG)

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. 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.

8.3.2.6. 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 Study Reference Manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

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

Refer to the Study Reference 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
Every Visit through the End of Double-Blind Treatment	• Blood alcohol content		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)		
Screening Tests Only	• HBsAg • Hepatitis C antibody • TSH • Vitamin B_{12} • Syphilis serology • Serum or urine hCG pregnancy test (as needed for women of child bearing potential, including at follow-up/early termination) • Drug screen		

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

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or 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.

8.3.2.7. Assessment of Suicidality

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

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

8.3.2.8. 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. If a pregnancy is reported, then the investigator should inform the Medical Monitor within 24 hours of learning 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 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.

8.3.3. Pharmacokinetics

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

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

- At Baseline (Visit 3), the PK blood sample should be taken after cognitive testing, ECG, and vital signs measurements have been performed, and the date and time of the previous dose of donepezil will be recorded. The actual date and time of sample collection will be recorded.
- At Visit 5 (Week 6), the PK blood sample should be taken after cognitive testing, ECG, and vital signs measurements have been performed, and the time of the last dose of double-blind IP will be recorded. The actual date and time of sample collection will be recorded.
- At Visit 6 (Week 12) subjects will be instructed not to take their dose of double-blind IP in the morning but wait until in the clinic, after 1 PK sample is collected (before dosing, but after cognitive testing, ECG, and vital signs measurements have been performed). Donepezil can be taken on the regular schedule. The date and time of the previous double-blind IP and donepezil doses will be recorded along with the actual date and time of the pre-dose sample collection at Visit 6.
- At Visit 7 (Week 18), the PK blood sample should be taken after cognitive testing, ECG, and vital signs measurements have been performed, and the time of the last dose of double-blind IP will be recorded. The actual date and time of sample collection will be recorded.
- At Visit 8 (Week 24), 1 PK blood sample will be collected after cognitive testing, ECG, and vital signs measurements have been performed. The date and time of the previous donepezil and double-blind IP doses will be recorded along with the actual date and time of sample collection.
- Unscheduled PK samples may be requested by Axovant Sciences or the Medical Monitor after discussion with investigators (e.g., in cases of suspected drug reactions).

The samples will be centrifuged and the resulting plasma stored. Further details with regard to shipping, collection, and processing of samples are provided in the Study Reference Manual.

Plasma analysis will be performed under the control of Axovant Sciences, the details of which will be included in the Study Reference Manual. Concentrations of RVT-101, RVT-101 metabolites, and donepezil will be determined in plasma samples using the currently approved

bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the Study Reference Manual).

Once the plasma has been analyzed for RVT-101 and/or donepezil, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

9. DATA MANAGEMENT

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

Management of clinical data will be performed in accordance with applicable Axovant Sciences 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

The primary statistical framework will be to demonstrate superiority of RVT-101 over placebo based on the ADAS-Cog-11 and ADCS-ADL change from baseline to Week 24.

The first null hypothesis is that there is no difference between RVT-101 and placebo, when added to stable donepezil, in the change from baseline in total ADAS-Cog-11 score at Week 24 in the Intent-to-Treat (ITT) Population. The first alternative hypothesis is that there is a difference between RVT-101 and placebo, when added to stable donepezil, in the change from baseline to Week 24 total ADAS-Cog-11 score in the ITT Population.

The second null hypothesis is that that there is no difference between RVT-101 and placebo, when added to stable donepezil, in the change from baseline in total ADCS-ADL score at Week 24 in the ITT Population. The second alternative hypothesis is that there is a difference between RVT-101 and placebo, when added to stable donepezil, in the change from baseline to Week 24 of ADCS-ADL score in the ITT Population.

The primary comparisons of interest will be performed at the 5% level of significance. All hypothesis tests will be 2-sided, with no correction for multiple comparisons.

10.2. Sample Size Considerations

The primary comparisons of interest are to compare RVT-101 to placebo at Week 24 for change from baseline in both ADAS-Cog-11 and ADCS-ADL. A sample size of 435 subjects per treatment group will allow a difference of 1.6 points between placebo and active treatment in the change from baseline in ADAS-Cog score to be detected with 95% power and a 0.05 significance level assuming an underlying standard deviation (SD) of 6.5.

This sample size will also allow a difference of 2 points between placebo and active treatment in the change from baseline in ADCS-ADL score to be detected with 90% power and a 0.05 significance level assuming an underlying SD of 9. Sample size estimates were based on data from study AZ3110866.

Both endpoints need to achieve a significance level of 0.05 to maintain an overall 5% significance level. Hence, the multiplicity issue associated with the trial having 2 primary endpoints is addressed as efficacy will only be concluded if both endpoints are significant.

Assuming a drop-out and missing data rate of approximately 25% up to Week 24, a total of approximately 1150 subjects will be randomized in a 1:1 ratio to RVT-101 or placebo.

The impact of baseline severity and possible sub-populations of milder and more moderate subjects is an important consideration of this study. Hence, a stratified randomization will be used to enroll subjects according to their baseline MMSE score in the groupings of 10-15 points, 16-20 points, and 21-26 points.

Two subgroups using MMSE score at baseline will be examined: moderate 10-20 and mild 16-26. The thresholds for randomization presented in Table 4 will be enforced.

Table 4. Baseline Mini Mental State Examination Stratification

Baseline MMSE Score	10-15	16-20	21-26
Target for recruited population	≤30%; ≥20%	≤60%; ≥40%	≤30%; ≥20%

The purpose of this ratio is to ensure that approximately 70% of the recruited population will contribute data to a data-defined subgroup analysis of either milder or more moderate subjects on ADAS-Cog-11 and/or ADCS-ADL. It is estimated that a difference from placebo of 1.6 points in ADAS-Cog-11 and 2.0 points in ADCS-ADL will be observable with approximately 80% power in a subgroup, which includes approximately 70% of subjects.

10.2.1. Sample Size Sensitivity

Based on study AZ3110866, the observed range of standard deviations for ADAS-Cog changes from baseline score was 6.13 to 6.37, and the range of observed standard deviations for ADCS-ADL changes from baseline was 8.84 to 9.36. The sample size calculation for this study used the SD of 6.5 for the ADCS-Cog endpoint and SD of 9 for the ADCS-ADL endpoint.

The robustness of the sample size calculations have been considered in order to assess the impact on the power of the study. Table 5 below shows the sensitivity of the required sample size to the assumptions used in the sample size calculation.

Table 5. Sample Size Estimates with Varying Expected Treatment Differences and Standard Deviations

	Expected Difference (RVT-101 vs. Placebo)	SD	Sample Size to have at least 90% Power	Sample Size to have at least 80% Power	Power with N=435
ADAS-Cog-11	1.6	6	297	222	97.5
	1.6	6.5	348	261	95.2
	1.6	7	403	302	92.1
ADCS-ADL	1.8	8.5	469	351	87.7
	1.8	9	526	393	83.9
	1.8	9.5	586	438	79.8
	2	8.5	380	285	93.4
	2	9	426	318	90.6
	2	9.5	475	355	87.4

Abbreviations: ADAS-Cog-11 = Alzheimer's Disease Assessment Scale – Cognitive Subscale-11; ADCS-ADL = Alzheimer's Disease Cooperative Study - activities of daily living; SD = standard deviation.

10.2.2. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

The ITT Population will consist of all subjects randomized to treatment who have taken at least 1 dose of investigational product and who have at least 1 post-baseline assessment. This will be the primary population used for the efficacy analysis.

The Per-Protocol (PP) Population will consist of those members of the ITT Population who have no major protocol violations. The PP Population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT Population. This population will be used for confirmatory analysis of the 2 primary efficacy variables and other cognitive and functioning endpoints. The PP Population will be identified prior to breaking the study blind.

The primary population for safety analyses will be the Safety Population, which will consist of all subjects who were randomized and took at least 1 dose of investigational product.

10.3.2. Interim Analysis

No interim efficacy analyses are planned.

10.4. Key Elements of Analysis Plan

All hypothesis tests and confidence intervals will be 2-sided at an alpha level of 5%.

For statistical analysis, center information will be pooled by geographical region or size. The method of grouping by center will be agreed upon prior to unblinding the study and outlined in the Statistical Analysis Plan (SAP).

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

10.4.1. Primary Efficacy Analyses

The primary analyses will be based on the ITT Population. In addition, analyses of the PP Population will be used to support the primary efficacy analysis.

Treatment comparisons between the RVT-101 and placebo groups in ADAS-Cog-11 and ADCS-ADL scores change from baseline at Week 24 will be analyzed using a mixed model for

repeated measures (MMRM) with restricted maximum likelihood estimation. This model corrects for dropout and accounts for the fact that measurements taken on the same subject over time tend to be correlated, by using all available information on subjects within the same covariate set to come up with an estimate of the treatment effect for a dropout-free population. No imputation of the missing values will be made or required and the data used in the analysis will be the actual observed responses at each visit. The statistical model will be fitted with terms for treatment group, visit, treatment by visit interaction, baseline score, baseline MMSE, and pooled center.

The interaction terms of baseline MMSE by visit will be evaluated and will be included in the model if appropriate. Details will be provided in the RVT-101 3001 SAP.

Primary inferences will be drawn from treatment differences for the changes from baseline derived from the MMRM models at Week 24. As additional supportive information, treatment differences for each post baseline visit will also be derived using the MMRM models. The estimated treatment difference for at each visit will be displayed in the summary of statistical analysis together with the 95% confidence interval and the associated p-value.

The nature of missing data will be explored and the extent of missing data will be summarized. Sensitivity analysis will be conducted to support the MMRM analysis. This will include analysis based on completer, and analyses based on complete datasets for Week 24 derived via imputation techniques using analysis of covariance (ANCOVA). Details on covariates for ANCOVA and missing data imputations will be provided in the SAP.

The relationship between ADAS-Cog-11, ADCS-ADL, and baseline severity will be investigated.

The primary comparisons will be performed separately by moderate (Baseline MMSE 10-20) and mild (Baseline MMSE 16-26) using the same MMRM model. Additional subgroups including gender, demographic, and other baseline characteristics may be performed. Further details will be given in the SAP.

10.4.2. Secondary Efficacy Analyses

Cognition and other efficacy endpoints:

- ADAS-Cog-13 scores change from baseline at Week 24
- CIBIC+ scores at Week 24
- NPI scores change from baseline at Week 24
- The DS change from baseline at Week 24
- Comparison of RVT-101 versus placebo for the above endpoints will be performed using a mixed model for repeated measures or analysis of covariance (ANCOVA), similar to the models described for the primary endpoint.

The relationship between endpoints and demographics/baseline characteristics will be investigated. The comparisons may be repeated by selected subgroups of interest, i.e., gender,

baseline severity based on MMSE score, and other baseline characteristics. Further details will be given in the SAP.

In addition, the between treatment comparisons on CIBIC+ based on the Week 24 Observed Case (OC) and Week 24 LOCF datasets using Cochran-Mantel-Haenszel test will be performed. The number and percentage of subjects in each category of CIBIC+ will also be summarized by visit for each treatment group.

10.4.3. Tertiary Efficacy Measures

The RUD Lite and the EQ-5D will be summarized descriptively by treatment. Treatment comparisons between RVT-101 and placebo will be analyzed using an analysis of covariance (ANCOVA) model. Details will be provided in the SAP.

10.4.4. Responder Analysis

In this trial the following responder definitions will be presented:

1. ADAS-Cog-11: Improvement by at least 3 points from baseline at Week 24
2. ADCS-ADL: No change or improvement from baseline at Week 24
3. CIBIC+: No change or improvement at Week 24
4. ADAS-Cog-11 composite: Simultaneously meeting the criteria for ADAS-Cog-11, CIBIC+, and ADCS-ADL

Alternative composite endpoints and definitions of responders may be explored. The percentage of responders and the difference in proportions compared to placebo will be presented. This data will be analyzed using logistic regression or Cochran–Mantel–Haenszel test. Further details will be given in the SAP.

10.4.5. Pharmacokinetic Analyses

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

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

No population PK analysis is planned for donepezil. Donepezil concentrations will be visually compared to literature steady state values (mean ± SD) (Tiseo et al, 1998):

5 mg C_{min} = 21.4 ± 3.8 and C_{max} = 34.1 ± 7.3 ng/mL

10 mg C_{min} = 38.5 ± 8.6 and C_{max} = 60.5 ± 10.0 ng/mL,

where C_{min} is the minimum (trough) concentration and C_{max} is the peak concentration

10.4.6. Pharmacokinetic / Pharmacodynamic Analyses

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

10.4.7. Safety Analyses

The safety analyses will be based on the Safety Population.

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

10.4.7.1. Adverse Events

AEs will be considered treatment-emergent (TEAEs) if they start or worsen after first dose of the double-blinded 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 Single-Blind Run-In Period, the Double-Blind Treatment Period, and the Follow-up Period.

10.4.7.2. 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.

10.4.7.3. 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.

10.4.7.4. 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 SAP.

10.4.8. Subgroup Analyses

The efficacy analyses will be performed for the following subgroups:

- Milder Population (Baseline MMSE 16-26)
- Moderate Population (Baseline MMSE 10-20)
- Female
- Male

Analyses of additional subgroups based on demographics and baseline characteristics will be described in the SAP.

10.4.9. 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 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 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 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 (i.e., not names) should be recorded, if permitted by national regulation, 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 new drug, and any other study information, remain the sole and exclusive property of Axovant Sciences during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Axovant Sciences. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 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 are listed in the Source Data Verification Plan, and should include sequential notes containing at least the following information for each subject:

- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in trial (including trial number);

- Trial discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well);
- Record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity);
- Concomitant medication (including start and end date, dose if relevant, 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 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.

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

11.1.6. Electronic Case Report Forms

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

11.1.7. Drug Accountability

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused 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, and the initials of the person dispensing the investigational product, in accordance with national regulation.

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. 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 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 regulatory agency(ies). Axovant Sciences will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

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

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

No such communication, presentation, or publication will include Axovant Sciences' confidential information (see Section 11.1.3).

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

11.2.3. Posting of Information on Publicly Available Clinical Trial Registers

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

11.3. Joint Investigator/Sponsor Responsibilities

11.3.1. Access to Information for Monitoring

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

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

11.3.2. Access to Information for Auditing or Inspections

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

11.3.3. Study Discontinuation

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 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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