vTv THERAPEUTICS LLC
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TITLE PAGE

CLINICAL TRIAL PROTOCOL

RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTICENTER STUDIES TO EVALUATE THE SAFETY AND EFFICACY OF AZELIRAGON AS A TREATMENT FOR SUBJECTS WITH MILD ALZHEIMER'S DISEASE AND IMPAIRED GLUCOSE TOLERANCE

Investigational Product:	**TTP488**
Investigational Product Name:	**azeliragon**
US IND Number:	**IND 68,445**
Health Canada File Number:	**TBD**
EudraCT Number:	**NA**
Protocol and Study Number:	**TTP488-305**
Clinical Phase:	**Phase 2/3**
Version and Date:	**29 APRIL 2019**

SIGNATURE CONFIRMATION PAGE

Investigational Product: **Azeliragon** (TTP488)

Study Number: TTP488-305

Protocol Title: **RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTICENTER STUDIES TO EVALUATE THE SAFETY AND EFFICACY OF AZELIRAGON AS A TREATMENT FOR SUBJECTS WITH MILD ALZHEIMER'S DISEASE AND IMPAIRED GLUCOSE TOLERANCE**

Protocol Dated: **29 APRIL 2019**

I have reviewed and approved of the protocol listed above.

Louis Kirby, M.D. 04-29-2019

Responsible Medical Officer — Signature — Date
vTv Therapeutics LLC

Imogene Dunn, Ph.D. Imogene Dunn 04-29-2019

Senior Vice President, Biometrics and Regulatory Affairs — Signature — Date
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Document Revision History

Document	Version Date	Summary of Changes
Original Protocol	29 April 2019	N/A

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PROTOCOL SYNOPSIS

Study Number: TTP488-305	**Phase: 2/3**	

Title of Study:
Randomized, double-blind, placebo-controlled, multicenter studies to evaluate the safety and efficacy of azeliragon as a treatment for subjects with mild Alzheimer's disease and impaired glucose tolerance

Objectives:

PART 1

The primary objective of this study is:

- To evaluate the impact of 6 months of treatment with oral azeliragon on cognitive performance

The secondary objectives of this study are:

- To evaluate the efficacy of azeliragon treatment on measures of function and activities of daily living
- To evaluate the efficacy of azeliragon treatment on complications of diabetes
- To evaluate the safety and tolerability of 6 months of azeliragon treatment
- To evaluate the effect of azeliragon treatment on biomarkers and markers of inflammation

PART 2

The primary objective of this study is:

- To evaluate the efficacy of 18 months of treatment with oral azeliragon on cognition and global function

The secondary objectives of this study are:

- To evaluate the safety and tolerability of azeliragon treatment.
- To evaluate the efficacy of azeliragon treatment on activities of daily living, behavior, and quality of life
- To evaluate the efficacy of azeliragon treatment on complications of diabetes
- To evaluate the effect of azeliragon treatment on biomarkers and markers of inflammation

Endpoints

PART 1

Primary Endpoint:

- Change from Baseline in the ADAS-cog14 at Month 6

Secondary Endpoints:

- Change from Baseline in the CDR-sb at Month 6
- Change from Baseline in the FAQ at Month 6
- Change from Baseline in the Amsterdam-IADL at Month 6
- Change from Baseline in eGFR at Month 6

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Safety Endpoints:

- Adverse events, clinical laboratory tests, vital signs, 12-lead ECG, C-SSRS

PART 2

Co-Primary Endpoints:

- Change from Baseline in the ADAS-cog14 at Month 18
- Change from Baseline in CDR-sb at Month 18

Secondary Endpoints:

- Responder status at Months 6, 12, and 18 based on the ADAS-cog14
- Change from Baseline in FAQ score at Month 18
- Change from Baseline in Amsterdam-IADL score at Month 18
- Change from Baseline in MMSE score at Month 18
- Change from Baseline in eGFR at Month 18
- Change from Baseline in whole brain volume at Month 18

Safety Endpoints:

- Adverse events, clinical safety laboratory tests, ECG, vital signs, C-SSRS

Exploratory Endpoints:

- Change from Baseline at Month 18 for measures of behavior and quality of life (NPI, DEMQOL-proxy)
- Change from Baseline at Months 3, 6, and 12 for the primary and secondary measurements: ADAS-cog14, FAQ, Amsterdam-IADL, CDR-sb, MMSE, NPI, DEMQOL-proxy.
- Change from Baseline in plasma concentrations of Aβ species at Month 18
- Change from Baseline in brain MRI (hippocampal, ventricular) volumetric measures at Month 18

Study Design:

TTP488-305 is a protocol that consists of two sequential, multi-center, randomized, double-blind, placebo-controlled, parallel group studies to evaluate the safety and efficacy of oral azeliragon 5 mg/day relative to placebo in approximately 300 subjects (100 Part 1, 200 Part 2) with mild AD (screening MMSE 21-26, baseline MMSE 19-27 and ADAS-cog14 score of ≥10) and impaired glucose tolerance (Screening HbA1c 6.5% -9.5%, inclusive). Eligible participants will be randomly assigned to azeliragon or placebo in a 1:1 randomization for a double-blind dosing period of 6 months (Part 1) or 18 months (Part 2). The Part 1 and Part 2 studies will have independently randomized, unique study populations.

The Part 1, 6-month, double-blind treatment portion of the study will include 5 clinic visits. The primary objective of the Part 1 portion is to evaluate the efficacy of 6 months of oral azeliragon on a measure of cognition (ADAScog14). Secondary objectives of Part 1 will be to evaluate the efficacy of 6 months of oral azeliragon on multiple measures of function to inform selection of a functional endpoint to serve as co-primary in Part 2, as well as the sample size required to adequately power the study to detect treatment effect on cognitive and functional measures in the study population. Upon completion of Part 1, a subject's participation is considered complete and they will not be permitted to participate in Part 2.

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The Part 2, 18-month, double-blind treatment portion of the study will include 9 clinic visits. Part 2 will enroll 200 subjects who will be randomized to receive oral azeliragon 5 mg/day or placebo in a 1:1 randomization.

Study Drug, Doses and Mode of Administration:

Azeliragon and matching placebo will be administered orally once daily.

- 5 mg azeliragon
- Placebo

Number of Study Participants Planned:

Part 1:

100 subjects in 2 treatment groups (approximately 50 subjects per arm)

Part 2:

200 subjects in 2 treatment groups (approximately 100 subjects per arm)

Subject Selection

Subject eligibility must be reviewed and documented by an appropriately qualified member of the Principal Investigator's (PI's) study team before participants are included in the study.

Inclusion Criteria

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally authorized representative) and caregiver/informant has been informed of all pertinent aspects of the study. Participants must be able to provide consent or assent (where this is in accordance with local laws, regulations and ethics committee policy) and consent/assent must be re-evaluated during the study at regular intervals.
2. Male or female subjects aged 50-85 years (inclusive) at Screening Visit.
3. Female subjects must be of non-child-bearing potential. Male subjects with female partners of childbearing potential must agree to acceptable birth control for the duration of the study and for 90 days thereafter.
4. If on pharmacological treatment for diabetes, must be on stable dose for at least 60 days prior to screening and remain stable through Baseline. There should be expectation that treatment and dose will remain stable during the study period.
5. Clinical diagnosis of probable Alzheimer's disease, consistent with the criteria from the 2011 National Institute on Aging and Alzheimer's Association workgroup [McKhann 2011], for at least 2 months prior to Screening. Evidence of progression must be documented in source documentation at the time of screening based on review of prior medical records and/or information gathered from the subject or caregiver/informant(s).
6. Mini-Mental State Exam (MMSE) score of 21-26 inclusive at Screening and 19-27 at Baseline.
7. CDR global score of 0.5 or 1 at Screening and Baseline.
8. ADAS-cog14 score of $\geq$ 10 at Screening and Baseline.

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9. Participant must be on a stable dose of a background cholinesterase inhibitor and/or memantine (approved by relevant health authority where trial is being conducted) at least 60 days prior to Screening and remain stable through Baseline. There must be agreement not to change the treatment or dose during the study period unless the investigator judges that the dose needs to be reduced or stopped due to a safety and/or tolerability reason.
10. Hemoglobin A1c (HbA1c) 6.5% - 9.5%, inclusive, at Screening.
11. Body mass index (BMI) 19.0 – 37.0 kg/m^2, inclusive, at Screening Visit and Baseline Visit.
12. Body weight at least 45.0 kg at Screening Visit and Baseline Visit.
13. Participants and caregiver/informants who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
14. The subject must have a reliable caregiver/informant with regular contact (i.e., 10 hours a week as combination of face-to-face visits and telephone contact acceptable) who will facilitate the subject's full participation in the study. Caregiver/informant must have sufficient subject interaction to be able to provide meaningful input into the rating scales administered in this study where caregiver/informant input is required, and evidence of this should be documented in source documentation. Participants who reside in assisted living facilities are permitted provided that they meet caregiver/informant criteria.
15. Participants and caregiver/informants must be able to read, write, and speak the language in which psychometric tests are provided with visual and auditory acuity (corrected) sufficient to allow for accurate psychometric testing.
16. Subject must be able to ingest oral medications.

Exclusion Criteria

Participants presenting with any of the following will be excluded from participation in the study.

1. Current evidence or history of neurological or any other illness that could contribute to dementia including, but not limited to, other neurocognitive disorders (e.g., Lewy body disease, fronto-temporal dementia, Parkinson disease), HIV cognitive impairment, head injury with loss of consciousness proximate to the onset of dementia, vitamin B12 deficiency (see Exclusion 3, below), or thyroid disease (unless adequately treated for at least 3 months with normalization of laboratory values).
2. Participants from a family with known autosomal dominant AD associated with mutations in APP, PS1 or PS2 genes or strongly suspected, but not yet identified mutations in APP, PS1 or PS2 genes, or Down's syndrome. Individuals from families with any number of late onset AD affected family members may participate in this study.
3. Vitamin B12 levels lower than laboratory reported normal limits (and remains below on repeat testing). Participants may be enrolled following the initiation of B12 therapy for 4 weeks prior to dosing and confirmed within normal limits upon repeat.
4. Evidence of neurologic deficits from a previous stroke or MRI changes consistent with multi-infarct dementia. Diagnosis or any history of cerebrovascular stroke, severe carotid stenosis, cerebral hemorrhage, intracranial tumor, subarachnoid hemorrhage that, as determined by the investigator, could either contribute to the patient's current cognitive or functional status, impair his/her ability to fully participate in the trial or that may impact his/her status during the course of the trial.

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5. Specific exclusionary brain MRI findings (as identified on the central MRI read) as determined by the investigator that could either significantly contribute to the patient's current cognitive or functional decline, impair his/her ability to fully participate in the trial or that may impact his/her status during the course of the trial. In any case, the following are exclusionary:
   a. 10 or more microhemorrhages, as identified by the central reading report.
   b. Grade three deep white matter changes (diffuse involvement of entire region) on the central reading report.
6. History of schizophrenia or late onset (after age 40) bipolar disorder. Current or recent (within 6 months prior to Screening) clinically relevant or unstable psychiatric disorder (e.g., major depressive disorder) that, per the investigator's judgment, could significantly contribute to the patient's current cognitive or functional decline, impair his/her ability to fully participate in the trial, or may impact his/her status during the course of the trial.
7. Serious suicide risk per the following criteria:
   a. Suicidal ideation associated with intent and/or plan within the previous year as indicated by a "yes" answer on Items 4 or 5 of the C-SSRS;
   b. History of suicidal behavior within the previous 10 years as indicated by a "yes" answer to any of the suicidal behavior items of the C-SSRS with a behavior occurring within the previous 10 years;
   c. Lifetime history of serious or recurrent suicidal behavior (serious is defined as actual lethality/medical damage score > 2 on Screening C-SSRS)
8. History of cancer within the last 5 years except adequately treated cervical carcinoma in-situ, cutaneous basal cell or squamous cell cancer, or non-progressive prostate cancer not requiring current treatment.
9. Participants with poorly controlled hypertension with or without existing therapy (ex: systolic≥140 mmHg or diastolic ≥90 mmHg with repeated measures) at Screening or Baseline. Subjects with repeated measures of systolic≥140 mmHg or diastolic ≥90 mmHg at Screening will be allowed to participate with management of blood pressure below the exclusionary levels with introduction of an allowable medication and the subject has been on the drug for 4 weeks prior to Baseline. Subjects with repeated measures of systolic ≥140 mmHg or diastolic ≥90 mmHg at Baseline will be excluded.
10. Participants with evidence or history of severe drug allergies (such as resulting in dyspnea or severe rash) or allergy to any constituents of the study drug as formulated.
11. Known history or current evidence of moderate to severe substance use disorder according to DSM-5 criteria within 1 year prior to Screening or a positive result on the drug screening test (unless due to a permitted concomitant medication [e.g., a benzodiazepine as a sleep aid]).
12. Subjects with pulmonary hypertension are excluded.
13. Previous participation and dosing in another clinical trial for Alzheimer's disease as follows:
    a. Exposure to putative disease modifying therapies within 1 year before Screening Visit is exclusionary, unless placebo treatment assignment is documented.
    b. Exposure to symptomatic therapy within 90 days (or five half-lives, whichever is longer) before Screening Visit is exclusionary.

    Any clinical trial (Alzheimer's or non-Alzheimer's) study visit within 90 days before the Screening Visit is exclusionary regardless of treatment assignment.

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14. Participants who are taking or are expected to use drugs known to be strong CYP2C8 inhibitors.
15. Participants receiving systemic steroids. Topical corticosteroid application to the skin is allowed, as are localized corticosteroid injections if administered no more than once every 6 months during the last year and are expected to be administered no more frequently during the study. Use of inhaled, intranasal or otic steroids are not excluded.
16. Participants receiving medications that may negatively affect cognitive function (e.g., antidepressants, antipsychotics, sedatives/anxiolytics) unless such medications have been taken at a stable dose for at least 4 weeks prior to enrollment (i.e., in the investigator's judgment, efficacy and tolerability have been optimized) and are expected to continue on a stable dose for the duration of the trial.
17. Prescription medical food (i.e., Axona) intended for the dietary management of the metabolic processes associated with Alzheimer's disease.
18. Participants may not donate blood within 8 weeks prior to enrollment and for 6 months after the last administration of study drug.
19. History of clinically significant or current unstable cardiac disease as determined by the PI and in consultation with the Sponsor. Examples of cardiac disease that would be exclusionary include 2nd degree or greater heart block without a pacemaker, sick sinus syndrome, ventricular tachycardia or fibrillation, sustained supraventricular tachycardia, symptomatic bradycardia, congenital long QT interval syndrome, atrial fibrillation, clinically significant angina/coronary artery disease, myocardial infarction in the past year, congestive heart failure, cardiomyopathy, myocarditis, left ventricular hypertrophy, valvular heart disease requiring treatment or life style modification. Subjects with atrial fibrillation on anticoagulant therapy and who have had no thromboembolic events or other referable cardiac events in the preceding 1 year are considered stable and may be screened.
20. Participants demonstrating QTcF > 470 msec on Screening 12-lead ECG (confirmed with a repeat measure). Participants with known history of bundle branch block (either right or left) are allowed if QTcF value does not exceed 500 msec. Participants with a functioning pacemaker, indicated by an ECG displaying paced rhythm, are allowed with no QTcF upper limit.
21. History of diabetic ketoacidosis within the last year.
22. History of more than one severe episode of hypoglycemia that required assistance by a third party within the past year.
23. History of chronic pancreatitis.
24. Current clinically significant hepatic disease or elevated LFTs $\geq$ 2 times the upper limit of normal (ULN) at Screening.
25. Stage 4 kidney disease (estimated GFR < 30 mL/min/1.73 m^2, as calculated by the CKD-EPI equation [Levey 2009]).
26. Any laboratory value not already specified above that is outside the laboratory reference range and considered by the Principal Investigator, or appropriately qualified designee, to be a clinically significant abnormality.
27. Use of insulin therapy.

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28. Any other medical condition or reason that, in the opinion of the Principal Investigator or appropriately qualified designee, makes the subject unsuitable to participate in this clinical trial.

Eligibility for randomization will be reviewed and approved by an independent Randomization Authorization Committee. The remit of this committee will be to ensure each patient deemed by the Investigator to be eligible for the trial meets key eligibility criteria and is suitable for participation in the study.

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Statistical Methods:

Population of Analysis:

The following population of analysis will be used for all statistical analysis:

- The full analysis set (FAS) includes all randomized subjects who receive any study medication and have at least one post-Baseline assessment.
- The per protocol set (PPS) includes all subjects in the FAS, except for those who are excluded because of major protocol violations, where a major protocol violation is one that may affect the interpretation of study results (e.g., taking less than 50% of prescribed study medication during participation).
- The safety set (SAF) includes all subjects who receive any study medication.

The FAS will be used for all hypothesis tests of efficacy. The PPS is used for supportive efficacy analysis.

The SAF will be used for safety analyses.

Sample size considerations for Part 1:

Assuming a standard deviation of the change from Baseline to Month 6 in ADAS-cog14 of 4, using alpha = 0.05, a total sample size of approximately 82 subjects in balanced allocation (41 subjects per group) provides at least 90% power to detect a difference between treatment groups of 2.9 using a 2-sided, 2-sample t-test. Assuming a dropout rate of 18% or less, randomization of 100 subjects provides adequate statistical power for Part 1 to demonstrate superiority of azeliragon over placebo based on the ADAS-cog14.

Sample size considerations for Part 2:

Assuming a standard deviation of the change from Baseline to Month 18 in ADAS-cog14 of 7.5, using alpha = 0.049, a total sample size of 120 subjects in balanced allocation (60 subjects per group) provides at least 90% power to detect a difference between treatment groups of 4.5 using a 2-sided, 2-sample t-test. Assuming a dropout rate of 25% or less, randomization of 160 subjects provides adequate statistical power for Part 2 to demonstrate superiority of azeliragon over placebo based on the ADAS-cog14.

Statistical methods:

The primary analysis will use the intent-to-treat (ITT) methodology and a main-effects model for analysis of covariance with baseline ADAS-cog14 as a covariate on change from baseline to endpoint in ADAS-cog14 using multiple-imputation methods for coping with missing data. The primary analysis will be supported by a mixed-models repeated measures (MMRM) analysis with adjustment for baseline ADAS-cog14 measures. Similar methodology will be used for the functional endpoints (CDR-sb, FAQ, Amsterdam IADL). The primary analysis will also be supported by ANCOVA using last-observation-carried-forward (LOCF) methods, and also an observed cases analysis (no imputation, no deletion) will be done. The supportive MMRM analysis will include treatment, time and treatment-by-time interaction as fixed effects, baseline as covariate and subject as a random effect. Supportive modeling will also include MMRM main-effects model with treatment, time, and subject. The same statistical methodology will be applied to the functional endpoints. A conditional sequence of statistical hypotheses will be used to control alpha with the ADAS-cog14 being tested first, and conditional on statistical significance, testing will proceed to CDR.

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Descriptive summaries will be produced of the observed values and change from baseline in co-primary variables by treatment group at each individual time point and at endpoint (final on-treatment assessment for each subject).

In accordance with FDA guidance on adaptive studies, the planned features of the confirmatory phase (Part 2) are pre-specified. The features subject to modification informed by the learning phase of the study (Part 1) are:

- Primary endpoint for Part 2
- Sample size for Part 2
- Study duration for Part 2
- Eligibility for Part 2
- Dose of study drug for Part 2

Table 1. Part 1 Schedule of Activities

	Screening	Baseline	Treatment Period[a]							Follow-up[b]
Protocol Activity	**Day -60 to Day -1**	**Day -7 to Day 1**	**Day 1[c]**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6 / ET**	**3 months after last dose**
Study Days	-60 to -1	-7 to 1	1	30	60	90	120	150	180 or ET	270
Window				±7d	±7d	±7d	±7d	±7d	±7d	±7d
Sign informed consent / provide assent[d]	X									
Assessment of continued consent/assent		X				X			X	X
Assign Screening ID	X									
Randomization			X							
Demographic information	X									
Review Inclusion/Exclusion Criteria	X	X	X							
Medical History/Surgical History / Drug, Alcohol, Tobacco Use History	X									
Complete Neuro Exam & Physical Exam	X									
Height	X									
ApoE genotyping		X								
Telephone Contact				X	X		X	X		
Body weight	X	X				X			X	X
BMI calculation	X									
Brief Neuro & Physical Exams		X				X			X	X
Review Concomitant Medications	X	X		X	X	X	X	X	X	X
Blood Pressure and Pulse Rate (supine) [e]	X	X[e]				X			X	X
12 Lead ECG[e]	X[f]	X[e]				X			X	X
Adverse Events Assessment		X		X	X	X	X	X	X	X

Table 1. Part 1 Schedule of Activities (continued)

Protocol Activity	Screening	Baseline	Treatment Period[a]							Follow-up[b]
	Day -60 to Day -1	Day -7 to Day 1	Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6 / ET	3 months after last dose
Study Days	-60 to -1	-7 to 1	1	30	60	90	120	150	180 or ET	270
Window				±7d	±7d	±7d	±7d	±7d	±7d	±7d
Dispense / Return Study Drug / Drug Accountability			X			X			X	
Study Drug Dosing[a,c]			X	→	→	→	→	→		
MMSE[g]	X	X				X			X[h]	X
ADAS-cog14[g]	X	X				X			X[h]	X
CDR[g]	X	X				X			X[h]	X
FAQ		X				X			X[h]	X
Amsterdam-IADL		X				X			X[h]	X
Columbia Suicide Severity Scale (C-SSRS)[i]	X	X				X			X	X
Fasting Central Lab Blood and Urine Collection[j]	X	X				X			X	X
Urine Drug Screen	X									
Provide meal/snack[k]	X	X				X			X	X
Blood glucose measurement[l]	X	X				X			X	X
Brain MRI[m]	X									
Blood Sample for PK, PD and Plasma Retention and Storage		X				X			X	X

Table 1. Part 1 Schedule of Activities (continued)

a Participants will receive azeliragon 5 mg once daily, or matching placebo during the treatment period.
b Follow-up visit required for all participants who dosed with study medication. A Follow-up Visit should be completed 3 months after a subject completes Month 6 for those participants who complete the study; or at least 45 days after the last dose of study drug if the subject discontinues the study prior to Month 6.
c Subject begins taking study medication in the clinic as soon as baseline procedures are completed, and eligibility confirmed. Date of first dose is noted as Day 1.
d Where assent is in accordance with local laws, regulations and ethics committee policy.
e Vitals and ECG will be measured in triplicate at Baseline and as single values at all other times. An average of the three measurements for ECG and blood pressure will be used for eligibility determination.
f ECG at Screening visit repeated if QTc > 470 msec.
g Neuropsychological assessments are not to be performed with fasted participant; ensure participant has been fed and meets blood glucose measurement requirements prior to any neuropsychological assessments.
h Neuropsychological assessments are performed at the Early Termination Visit only when the visit is within 30 days of the last dose of study drug.
i C-SSRS is administered to subject jointly with caregiver.
j Blood Chemistry sample is collected in a fasted state (8-hour fast).
k Provide a low carbohydrate/high protein meal or snack *after* fasting blood samples are drawn and *before* any neuropsychological assessments are performed.
l Blood glucose measurement is an in-office point of care measurement after an appropriate period following the meal/snack, and prior to neuropsychological assessments are performed.
m CT scan may be utilized for subjects with contraindication to MRI. MRI or CT should be done at least 14 days prior to the baseline visit to allow time for MRI report to support eligibility decision.

Table 2. Part 2 Schedule of Activities

	Screening	Baseline	Treatment Period[a]									Follow-up[b]
Protocol Activity	**Day -60 to Day -1**	**Day -7 to Day 1**	**Day 1[c]**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18 /ET**	**3 months after last dose**
Study Days	-60 to -1	-7 to 1	1	30	60	90	180	270	360	450	540 or ET	630
Window				±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	± 7d
Sign informed consent / provide assent[d]	X											
Assessment of continued consent/assent		X				X	X	X	X	X	X	X
Assign Screening ID	X											
Randomization			X									
Demographic information	X											
Review Inclusion/Exclusion Criteria	X	X	X									
Medical History / Surgical History / Drug, Alcohol, Tobacco Use History	X											
Complete Neuro Exam & Physical Exam	X											
Height	X											
ApoE genotyping		X										
Telephone contact				X	X							
Body weight	X	X				X	X	X	X	X	X	X
BMI calculation	X											
Brief Neuro & Physical Exams		X				X	X	X	X	X	X	X
Review Concomitant Medications	X	X		X	X	X	X	X	X	X	X	X
Blood Pressure and Pulse Rate (supine)	X	X				X	X	X	X	X	X	X

Table 2. Part 2 Schedule of Activities (continued)

Protocol Activity	Screening	Baseline	Treatment Period[a]									Follow-up[b]
	Day -60 to Day -1	Day -7 to Day 1	Day 1[c]	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18 /ET	3 months after last dose
Study Days	-60 to -1	-7 to 1	1	30	60	90	180	270	360	450	540 or ET	630
Window				±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	± 7d
12 Lead ECG[e]	X[f]	X[e]				X	X	X	X	X	X	X
Adverse Events Assessment		X		X	X	X	X	X	X	X	X	X
Dispense / Return Study Drug / Drug Accountability			X			X	X	X	X	X	X	
Study Drug Dosing[a,c]			X	→	→	→	→	→	→	→		
MMSE[g]	X	X				X	X	X	X	X	X[h]	X
ADAS-cog14[g]	X	X				X	X	X	X	X	X[h]	X
CDR[g]	X	X				X	X		X		X[h]	X
FAQ		X				X	X		X		X[h]	X
Amsterdam-IADL		X				X	X		X		X[h]	X
NPI		X				X	X		X		X[h]	X
DEMQOL-proxy		X				X	X		X		X[h]	X
Columbia Suicide Severity Scale (C-SSRS)[i]	X	X				X	X	X	X	X	X	X
Fasting Central Lab Blood and Urine Collection[j]	X	X				X	X	X	X	X	X	X
Urine Drug Screen	X											
Provide meal/snack[k]	X	X				X	X	X	X	X	X	X
Blood glucose measurement[l]	X	X				X	X	X	X	X	X	X
Brain MRI[m]	X										X	
Blood Sample for PK, PD, and Plasma Retention and Storage		X				X	X	X	X	X	X	X

Table 2. Part 2 Schedule of Activities (continued)

a Participants will receive azeliragon 5 mg once daily, or matching placebo during the treatment period.
b Follow-up visit required for all participants who dosed with study medication. A Follow-up Visit should be completed 3 months after a subject completes Month 18 for those participants who complete the study; or at least 45 days after the last dose of study drug if the subject discontinues the study prior to Month 18.
c Subject begins taking study medication in the clinic as soon as baseline procedures are completed, and eligibility confirmed. Date of first dose is noted as Day 1.
d Where assent is in accordance with local laws, regulations and ethics committee policy.
e Vitals and ECG will be measured in triplicate at Baseline and as single values at all other times. An average of the three measurements for ECG and blood pressure will be used for eligibility determination.
f ECG at Screening visit repeated if QTc > 470 msec.
g Neuropsychological assessments are not to be performed with fasted participant; ensure participant has been fed and meets blood glucose measurement requirements prior to any neuropsychological assessments.
h Neuropsychological assessments are performed at the Early Termination Visit only when the visit is within 30 days of the last dose of study drug.
i C-SSRS is administered to subject jointly with caregiver.
j Blood Chemistry sample is collected in a fasted state (8-hour fast).
k Provide a low carbohydrate/high protein meal or snack *after* fasting blood samples are drawn and *before* any neuropsychological assessments are performed.
l Blood glucose measurement is an in-office point of care measurement after an appropriate period following the meal/snack, and prior to neuropsychological assessments are performed.
m CT scan may be utilized for subjects with contraindication to MRI. MRI or CT should be done at least 14 days prior to the baseline visit to allow time for MRI report to support eligibility decision.

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LIST OF ABBREVIATIONS

Aβ	Aβ peptide fragment of the amyloid precursor protein
AD	Alzheimer's Disease
ADAS-cog14	Alzheimer's Disease Assessment Scale – Cognitive Subscale - 14 Item
AE	Adverse Event
AGE	Advanced Glycation Endproduct
A-IADL	Amsterdam Instrumental Activities of Daily Living questionnaire
ALT	Alanine Aminotransferase
APP	Amyloid Precursor Protein
AST	Aspartate Aminotransferase
BBB	Bundle branch block
BMI	Body mass index
BUN	Blood Urea Nitrogen
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale-Sum of Boxes
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed Tomography
DEMQOL	Health-Related Quality of Life for People with Dementia
DILI	Drug Induced Liver Injury
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 4th ed Text Revision
ECG	Electrocardiogram
EDC	Electronic data capture
FAQ	Functional Assessment Questionnaire
FAS	Full analysis set
FDR	Food and Drug Regulations
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
HbA1c	Hemoglobin A1c
HDPE	High density polyethylene
HIS	Heat induction seal
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate Dehydrogenase
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Methylmalonic Acid
MMSE	Mini-Mental State Exam
MRI	Magnetic Resonance Imaging
NASH	Nonalcoholic Steatohepatitis
NPI	Neuropsychiatric Inventory Questionnaire
PD	Pharmacodynamic
PI	Principal Investigator

LIST OF ABBREVIATIONS (continued)

PK	Pharmacokinetic
PPS	Per-protocol set
RAGE	Receptor for Advanced Glycation Endproducts
REB	Research Ethics Board
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SoC	Standard of care
SUVR	Standardized uptake value ratio
T2DM	Type 2 diabetes
TAS	Target analysis set
TEAE	Treatment-Emergent Adverse Event
TEAV	Treatment-Emergent Abnormal Value
TSH	Thyroid Stimulating Hormone
TTP488	Azeliragon
UA	Urinalysis
ULN	Upper Limit of Normal
QD	Taken Once Daily
QTcF	QT interval calculated using Fridericia's correction factor
WHODD	WHO Drug Dictionary

1.0 INTRODUCTION

These studies are designed to evaluate the safety and efficacy of azeliragon as a treatment for subjects with mild Alzheimer's disease and impaired glucose tolerance.

1.1 BACKGROUND AND RATIONALE

1.1.1 Dementia and Diabetes

Worldwide there are currently approximately 35.6 million people with dementia.(Alzheimer's Association 2016) There is an estimated 98 million people (65-79 years-old) who have diabetes.(International Diabetes Federation 2017) In the absence of a treatment that slows or halts the progression of cognitive and functional decline, AD often seriously impacts patients and their families as well as the healthcare economy. This is true in the AD population generally, but also among those with both AD and diabetes.

Numerous studies have suggested a link between type 2 diabetes and cognitive decline, mild cognitive impairment, and dementia.(Dhananjayan 2018) Type 2 diabetes may be present in up to 35% of people with Alzheimer's disease.(Janson 2004) Recently, a linear correlation between circulating HbA1c levels and cognitive decline has been observed in the English Longitudinal Study of Ageing.(Zheng 2018) It is also estimated that, in the United States, nearly 40 percent of Medicare beneficiaries age 65 and older with dementia also have diabetes.(Alzheimer's Association. 2018) Given the prevalence of type 2 diabetes and dementia in the most rapidly-growing segment of the population, there is a significant unmet medical need.

An overproduction of amyloid beta (Aβ) has been implicated as the leading mechanistic factor in AD pathology. Aβ is known to bind to the receptor for advanced glycation endproducts (RAGE), an immunoglobulin supergene family member expressed on multiple cell types in the brain and the periphery.(Yan 1996, Stern 2002) RAGE is expressed at low levels in many healthy tissues (except skin and mucus membranes) and is prominently expressed on endothelial cells and microglia of the neurovascular compartment. RAGE ligands include Aβ, S100b, HMGB1, and Advanced Glycation Endproducts (AGEs). Increases in the

concentration of RAGE ligands induce RAGE expression. RAGE-ligand interactions lead to sustained inflammatory states that play a role in chronic diseases, including diabetes, inflammation, and AD.(Stern 2002, Bierhaus 2005) RAGE has been proposed to contribute to AD pathology by: promoting inflammation, vascular leakage, and influx of peripheral Aβ into brain; mediating Aβ induced oxidative stress and Aβ- mediated neuronal death.(Dean 2003, Carrano 2011, Hartz 2012, Kook 2012) Additionally, RAGE is believed to be involved in mediating advanced glycation endproduct-induced tau hyperphosphorylation.(Li 2012) In AD, increases in RAGE protein and percentage of RAGE-expressing microglia parallel the severity of disease.(Yan 1996)

AGEs accumulate in tissues of people with type 2 diabetes playing a major role in worsening of complications of type 2 diabetes, such as retinopathy, neuropathy and nephropathy. When the concentration of RAGE ligands (e.g., AGEs) increase, more RAGE expression is induced.(Bierhaus 2005) Furthermore, AGE accumulation parallels the development of cognitive impairment and dementia in individuals with type 2 diabetes.(Dhananjayan 2018)

1.1.2 Mechanism of Action

Azeliragon is an orally bioavailable inhibitor of the receptor for advanced glycation endproducts (RAGE) being developed by vTv.

In transgenic mouse models of AD, azeliragon is associated with less neuroinflammation (TNF-α. TGF-β. IL-1) and Aβ deposition in the brain, improvement in cerebral blood flow and glucose uptake in the brain, and preservation of cognitive / behavioral performance compared to control animals. Azeliragon has also been shown, in animal models of type 2 diabetes, to reduce inflammatory markers with improvement in wound healing (endothelial cell extension), diabetic retinopathy (microvascular trees comparable to control) and nephropathy (improved sclerotic lesions).

Recent exploratory analyses of azeliragon from the STEADFAST Phase 3 studies provide preliminary clinical evidence that patients with increased concentrations of RAGE ligands may benefit from azeliragon.

These data taken together suggest that inhibition of RAGE with an orally available small molecule inhibitor, such as azeliragon, presents an attractive therapeutic rationale for the treatment of Alzheimer's dementia in patients with impaired glucose tolerance.

1.1.3 Clinical Studies

The azeliragon clinical development program to date consists of eight Phase 1 studies in the USA, three Phase 2 studies in North America (US and Canada), two Phase 3 studies (operationally conducted under one protocol) and an open-label extension study conducted globally, described in the Investigator's Brochure.

vTv recently completed two Phase 3 studies (under protocol TTP488-301, STEADFAST A-Study and STEADFAST B-Study) examining the effect of azeliragon on both cognitive (i.e., ADAS-cog11) and functional (i.e., CDR-sb) outcomes in patients with mild dementia of the Alzheimer's disease type. The trial was a randomized, double-blind, placebo-controlled trial in 880 participants with probable mild AD, MMSE 21-26 at screening, CDR 0.5 or 1, receiving stable standard of care (acetylcholinesterase inhibitor and/or memantine) evaluating the efficacy and safety of 18 months of treatment with azeliragon 5 mg/day relative to placebo. The clinical trial design included two separate, identical studies (A-Study and B-Study) operationally conducted under a single protocol. Each study was independently powered to evaluate efficacy with respect to co-primary endpoints of ADAS cog11 and CDR-sb and were randomized separately. Patients were randomized 1:1 (site-based randomization) to azeliragon (5 mg/day) or placebo. The A-Study was conducted in North America (US and Canada). The B-Study was global, conducted in North America (US and Canada), Ireland, UK, South Africa, Australia and New Zealand.

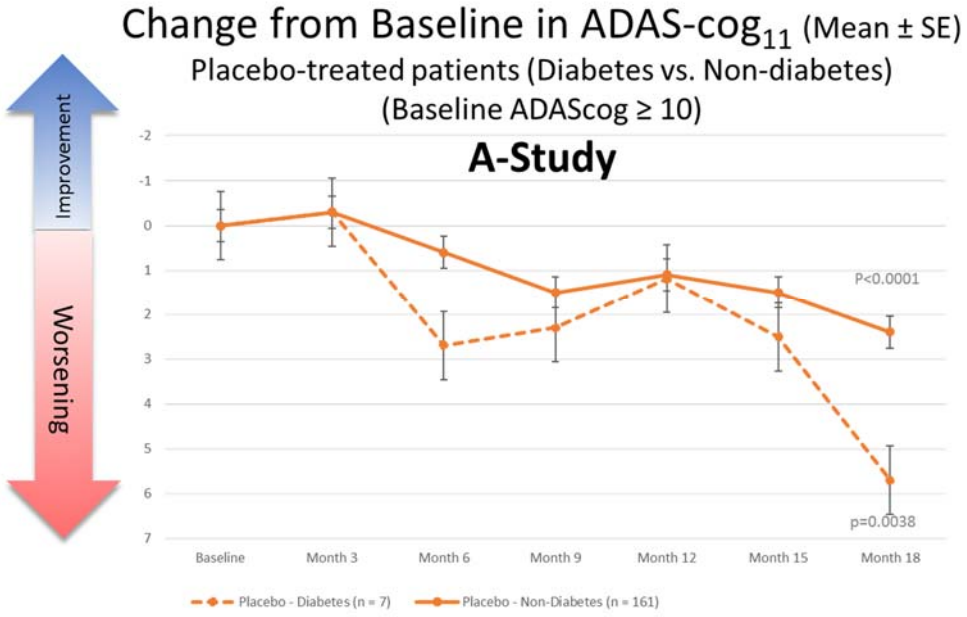
Topline results from the STEADFAST A-Study failed to demonstrate a beneficial effect of azeliragon on the protocol specified primary endpoints. As a result, the ongoing studies (including the B-Study) were terminated, databases locked, and data analyzed. Although the STEADFAST A-Study and B-Study did not achieve statistical significance on either of the co-primary endpoints, important results were obtained through post-hoc subgroup analysis that warrant additional investigation.

Further examination of the data showed clear differences in rate of placebo decline in ADAS-cog between the STEADFAST study (3 points in 18 months), the azeliragon Phase 2b study (10 points in 18 months) and that published for other similar studies (6 points in 18 months [Thomas 2016]), which may explain the lack of detectable effect in the STEADFAST study (the study was powered to detect a 4 point difference in change from baseline between active and placebo at 18 months, assuming a placebo decline of approximately 6 points over 18 months). It is hypothesized that subjects with higher expression of RAGE would present more inflammation and neurodegeneration and decline at a faster rate.

It has been demonstrated that advanced glycation endproducts accumulate in tissues of patients with diabetes with expression of RAGE increasing in response to injury and increases in ligand concentrations, including AGEs. This interaction of AGEs, and other ligands of RAGE, leads to sustained cellular damage and inflammation thus contributing to complications of diabetes including retinopathy, neuropathy and nephropathy. Further it has been shown that accumulation of AGEs parallels the development of cognitive impairment and dementia in patients with diabetes. Thus, patients with diabetes represent a sub-group expected to have increased concentration of RAGE ligands, increased expression of the RAGE receptor, have the potential to decline at a more rapid rate and thereby likely to respond to an antagonist of RAGE.

A comparison of placebo-treated subjects in the diabetic subgroup (defined as HbA1c $\geq$ 6.5%) and the non-diabetic (HbA1c < 6.5%) complement of the target analysis set (subjects with evidence of cognitive impairment at Baseline [ADAScog $\geq$ 10]) is provided in Figure 1. Interestingly, the data show a clear difference in the rate of cognitive decline between the placebo subjects with diabetes and the placebo subjects without diabetes. The diabetic, placebo-treated subjects had numerically greater decline from baseline in the ADAS-cog when compared with the non-diabetic, placebo treated subjects. These data further support the hypothesis that subjects with presumed higher expression of RAGE present more inflammation and neurodegeneration and decline at a faster rate.

Figure 1. Change from Baseline in ADAS-cog: Comparison of Placebo-treated patients with HbA1c at Baseline ≥ 6.5% and HbA1c < 6.5% (TTP488-301 A-Study [Target Analysis Set])



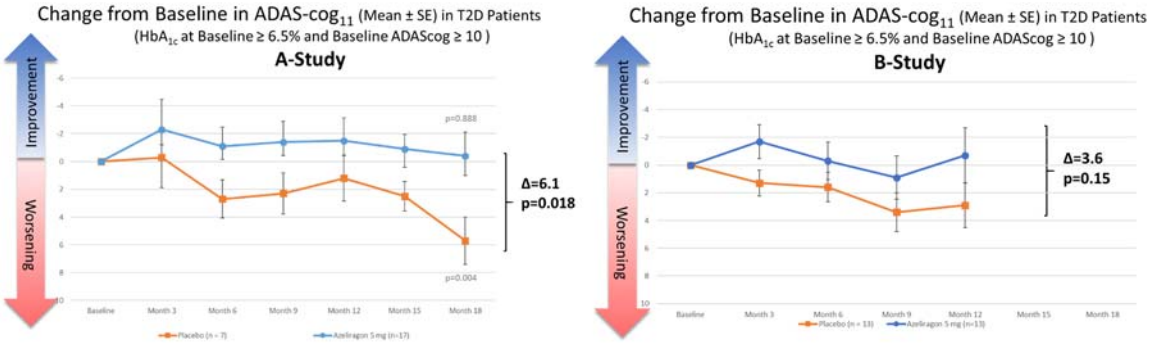
*p values are relative to each population's Baseline.

A subpopulation of STEADFAST participants with probable Alzheimer's disease and type 2 diabetes was evaluated during post hoc, exploratory, subgroup analyses of the STEADFAST Study. Patients with type 2 diabetes were selected because they are known to have increased levels of AGEs; and increased levels of AGEs are known to induce RAGE expression. Therefore, HbA1c was chosen as a surrogate for identifying individuals with elevated levels of AGEs and high RAGE expression. Based on the hypothesis that subjects with presumed increased expression of RAGE would demonstrate enhanced effects from a RAGE antagonist, the subgroup was defined as those STEADFAST participants with Baseline HbA1c ≥ 6.5%. The objective of the subgroup analysis was to determine if a differential response to azeliragon was observed in patients with increased HbA1c.

Twenty-four subjects (17 azeliragon and 7 placebo) in the STEADFAST A-study dataset were identified as the Target Analysis Set (TAS). The TAS represents the intended subject population for future studies and is defined as subjects with HbA1c ≥ 6.5% at Baseline and evidence of cognitive impairment at Baseline (ADAS-cog ≥ 10). Twenty-six subjects (13 azeliragon and 13 placebo) in the STEADFAST B-

study were identified as the TAS with Baseline HbA1c ≥ 6.5% and ADAS-cog ≥ 10. Unfortunately, the B-study was terminated by the sponsor and limited data are available beyond Month 9 for this subgroup. Figure 2 displays the Change from Baseline in ADAS-cog11 for the A-Study and B-Study in the TAS.

Figure 2. Change from Baseline in ADAS-cog: Type 2 Diabetic Subgroup (TTP488-301 [Target Analysis Set])



Results from the A-Study that completed the 18-month treatment period as planned, show a clear delineation between azeliragon and placebo groups in ADAS-cog throughout the duration of the study; separation achieves nominal statistical significance at multiple timepoints throughout treatment. The azeliragon-treated group (n=17) demonstrated a 3.8-point benefit on ADAS-cog relative to the placebo group (n=7) at Month 6, which was nominally statistically significant (p = 0.009). The azeliragon-treated group went on to demonstrate a 6.1-point benefit on ADAS-cog relative to the placebo group at Month 18, which was nominally statistically significant (p = 0.018).

Results from the B-Study that terminated after approximately 12 months of treatment, show numerical values on ADAS-cog change from baseline favoring azeliragon. The azeliragon-treated group (n=13) demonstrated a 1.9-point benefit on ADAS-cog relative to the placebo group (n=13) at Month 6. The azeliragon-treated group went on to demonstrate a 3.6-point benefit on ADAS-cog relative to the placebo group at Month 12.

Change from Baseline in CDR-sb was evaluated for the A-Study and B-Study in the TAS. Results from the A-Study that completed the 18-month treatment period as planned, show a clear delineation between azeliragon and placebo groups in

CDR-sb. The azeliragon-treated group (n=17) demonstrated a 1.7-point benefit on CDR-sb relative to the placebo group (n=7) at Month 18 (p = 0.05).

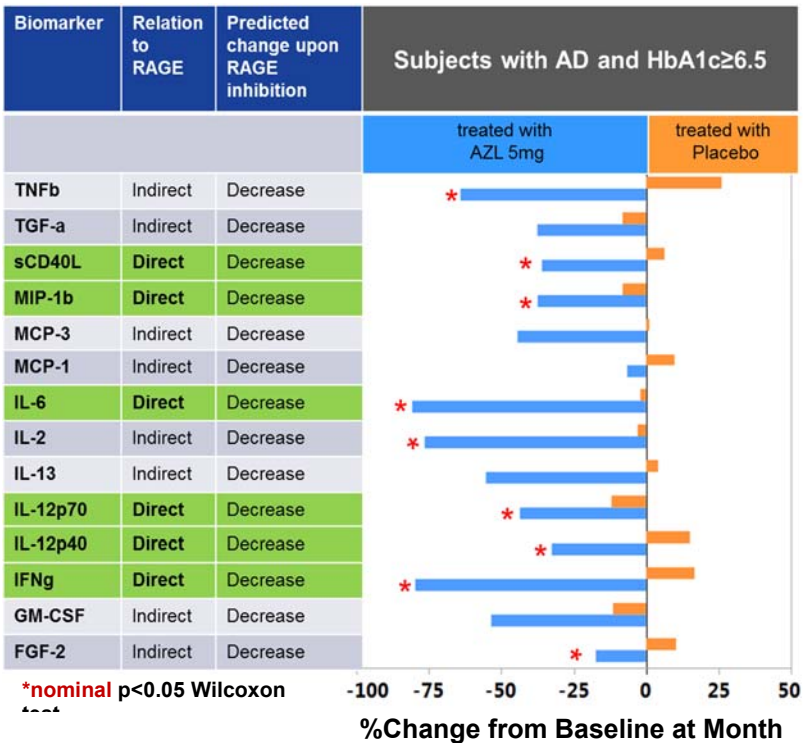
CDR-sb results from the B-Study are difficult to interpret. The planned study duration of 18 months was intended to allow sufficient time to see decline in the functional measure. Unfortunately, the B-study was terminated prematurely by the sponsor and limited data are available beyond Month 6 for the B Study type 2 diabetic subgroup. In the B-Study at Month 12, the azeliragon-treated group (n=13) demonstrated a 1.5-point change from Baseline while the placebo-treated group (n=13) had a 0.8-point change from Baseline. The inherent variability of the CDR-sb measure combined with the small sample size and shorter study duration for subjects in the B study has limited the interpretation of the functional endpoint in the B-Study.

The subgroup analysis of the STEADFAST Study showed cognitive benefit of azeliragon treatment in the subset of patients with probable AD and type 2 diabetes (as determined by HbA1c $\geq$ 6.5%). In support of the biological hypothesis for pursuing further development in patients with Alzheimer's dementia and type 2 diabetes, analyses were performed on changes in brain volumetric MRI, brain FDG PET, plasma RAGE related inflammatory markers, and glycemic control in patients that completed the 18-month study. The brain volumetric MRI data show favorable trends for less whole brain atrophy and less ventricular enlargement in the azeliragon-treated subgroup with HBA1c $\geq$6.5%. FDG PET data (standardized uptake value ratio [SUVR] for the mean composite region defined as unweighted combination of frontal, anterior/posterior cingulate, lateral parietal, lateral temporal and hippocampus) show trends for smaller decrements in glucose uptake (SUVR) in the azeliragon-treated subgroup with HBA1c $\geq$6.5%. Acknowledging the small sample sizes in the subgroup, the treatment differences in the type 2 diabetic subgroup (HbA1c $\geq$6.5%) are more robust than the overall study population.

Furthermore, a decrease in several plasma inflammatory biomarkers was observed in the type 2 diabetic subgroup patients treated with azeliragon in the A-Study. The biomarker panel data (Figure 3) show significant decreases from Baseline to Month 18 in the azeliragon group in IL-6, IL 12, INFγ, CD40L, MIP-1β, IL-2 and TNFβ, and FGF-2; the data also show strong trends toward a decrease in IL 13, TGFα, MCP-3 MPC-1 and CSF2 in the azeliragon group. These inflammatory biomarkers

are those associated with RAGE activation and are contributors to the neuroinflammation signaling pathway. The decrease in several plasma inflammatory biomarkers in the azeliragon-treated group provides further biological evidence of a treatment response in this subpopulation.

Figure 3. Changes in Inflammatory Biomarker Profile: Type 2 Diabetic Subgroup (TTP488-301 A-Study [FAS completers])



The observed cognitive benefit of azeliragon in a subgroup of AD patients with co-existing type 2 diabetes is supported by biological evidence of response including MRI, FDG-PET, and biomarker data. Furthermore, the subgroup findings are consistent with the biology of RAGE and the mechanism of action of azeliragon. It is biologically plausible that blocking RAGE-ligand interactions in this population, with azeliragon, can result in a robust beneficial effect. These results warrant further investigation to confirm azeliragon is a potential therapeutic approach for the treatment of patients with Alzheimer's disease and impaired glucose tolerance.

The present study has been designed to evaluate the efficacy of azeliragon in subjects with mild Alzheimer's disease and impaired glucose tolerance, defined as HbA1c ≥6.5%.

1.1.4 Dose Selection Rationale

The azeliragon dose (5 mg daily) for the current study was selected following review of single- and multiple-dose PK, pharmacodynamics (PD), and safety data, and the clinical efficacy data from the Phase 2 study (TTP488-203) and the Phase 3 study (TTP488-301).

The decision to advance a 5mg dose into Phase 3 was based on exploratory analyses relating azeliragon trough concentrations to ADAS-cog values and changes in ADAS-cog utilized a subject-level concentration value derived by 2 methods: (1) the maximum of the trough concentration values for that subject over the 18-month period, and (2) the median concentration value for that individual. Analyses were done at the subject level. Each subject's value was analyzed using descriptive statistics. A summary of the results is found in Table 3.

Table 3. Descriptive Statistics on Trough Concentrations

Concentration Value for Each Subject	Azeliragon Dose Group	Mean Concentration for Dose Group (each subject contributes a single value)	Median Concentration for Dose Group (each subject contributes a single value)	95% Confidence Interval of the Mean
Median of trough values	15/5 mg (n = 131)	13.02	12.25	[11.74, 14.31]
	60/20 mg (n = 134)	68.57	64.58	[63.46, 73.69]
Maximum of trough values	15/5 mg (n = 131)	16.22	14.90	[14.59, 17.85]
	60/20 mg (n = 134)	83.75	75.05	[77.40, 90.10]

Participants were subsequently classified into concentration groups according to cut-points in the distribution of trough concentration values ignoring administered dose. To assess the sensitivity of analysis results to the choice of cut-points, analysis included the following cuts:

- Tertile
- Quartile
- Quintile
- Decile

Results of analyses of the 4 classification schemes were consistent. Results indicated that within certain trough concentration ranges, delineation from placebo in changes in ADAS- cog at 18 months for azeliragon was more pronounced than in other ranges. As expected, higher trough concentrations tended to be observed for participants in the 20 mg dose group, and lower trough concentrations tended to be observed for participants in the 5 mg dose group.

Exploratory analysis of concentration-driven assessment of PK/PD effects included the quantile cuts described above and also iterative analysis focused on identification of a concentration range that was associated with optimal effectiveness for efficacy measures (primary and secondary measures). The iterative analysis included construction of groups with minimum trough concentrations ranging from 1 to 20 ng/ml. Within these groups, ranges were derived using optimization techniques to identify concentration groups that maximized efficacy. The results of the exploratory PK/PD analysis concluded that the optimal trough concentration range was 8-15 ng/ml over the 18-month period.

Based on the considerations outlined above, a 5 mg/day dose was selected. Doses below 5 mg/day and between 5 mg/day and 20 mg/day were considered. Doses below 5 mg/day are expected to provide non-efficacious concentrations. Doses above 5 mg/day (ex: 10 mg/day) are not expected to provide significantly improved efficacy relative to the potential for achieving concentrations associated with acute, reversible cognitive worsening.

The effect of food on the pharmacokinetics of azeliragon was evaluated in the TTP488-105 study. There was an approximately 20% reduction in exposure (C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}72}$) following administration of a single 5 mg dose of azeliragon following a standard FDA high fat breakfast compared to dosing in the fasted state. Fed subjects experienced a greater lag time for absorption as compared to fasted subjects (median T_{lag} of 4 hours versus 1 hour post-dosing, respectively); however, the median T_{max} was the same between treatment groups (16 hours post-dosing). Therefore, azeliragon may be administered without regard to food.

1.1.5 Single Reference Safety Document

The single reference safety document for this protocol is the Investigators Brochure.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 OBJECTIVES

2.1.1 Part 1

Primary objective:

The primary objective of this study is to evaluate the impact of 6 months of treatment with oral azeliragon on cognitive performance.

Secondary objectives:

- To evaluate the efficacy of azeliragon treatment on measures of function and activities of daily living
- To evaluate the efficacy of azeliragon treatment on complications of diabetes
- To evaluate the safety and tolerability of 6 months of azeliragon treatment
- To evaluate the effect of azeliragon treatment on biomarkers and markers of inflammation

2.1.2 Part 2

Primary objective:

The primary objective of this study is to evaluate the efficacy of 18 months of treatment with oral azeliragon on cognition and global function.

Secondary objectives:

- To evaluate the safety and tolerability of azeliragon treatment
- To evaluate the efficacy of azeliragon treatment on activities of daily living, behavior, and quality of life
- To evaluate the efficacy of azeliragon treatment on complications of diabetes
- To evaluate the effect of azeliragon treatment on biomarkers and markers of inflammation

2.2 ENDPOINTS

2.2.1 Part 1

Primary Endpoint:

- Change from Baseline in the ADAS-cog14 at Month 6

Secondary Endpoints:

- Change from Baseline in the CDR-sb at Month 6
- Change from Baseline in the FAQ at Month 6
- Change from Baseline in the Amsterdam-IADL at Month 6
- Change from Baseline in eGFR at Month 6

Safety Endpoints:

- Adverse events, clinical laboratory tests, vital signs, 12-lead ECG, C-SSRS

2.2.2 Part 2

Co-Primary Endpoints:

- Change from Baseline in the ADAS-cog14 at Month 18
- Change from Baseline in CDR-sb at Month 18

Secondary Endpoints:

- Responder status at Months 6, 12, and 18 based on the ADAS-cog14
- Change from Baseline in FAQ score at Month 18
- Change from Baseline in Amsterdam-IADL score at Month 18
- Change from Baseline in MMSE score at Month 18
- Change from Baseline in eGFR at Month 18
- Change from Baseline in whole brain volume at Month 18

Safety Endpoints:

Adverse events, clinical safety laboratory tests, ECG, vital signs, C-SSRS

Exploratory Endpoints:

- Change from Baseline at Month 18 for measures of behavior and quality of life (NPI, DEMQOL-proxy)
- Change from Baseline at Months 3, 6, and 12 for the primary and secondary measurements: ADAS-cog14, FAQ, Amsterdam-IADL, CDR-sb, MMSE, NPI, DEMQOL-proxy
- Change from Baseline in plasma concentrations of Aβ species at Month 18
- Change from Baseline in brain MRI (hippocampal, ventricular) volumetric measures at Month 18

3.0 STUDY DESIGN

TTP488-305 is a protocol that consists of two sequential, multi-center, randomized, double-blind, placebo-controlled, parallel group studies to evaluate the safety and efficacy of oral azeliragon 5 mg/day relative to placebo in approximately 300 subjects (100 Part 1, 200 Part 2) with mild Alzheimer's disease (screening MMSE 21-26, baseline MMSE 19-27 and ADAS-cog14 score of ≥ 10) and impaired glucose tolerance (Screening HbA1c 6.5% -9.5%, inclusive). Eligible participants will be randomly assigned to azeliragon or placebo in a 1:1 randomization for a double-blind dosing period of 6 months (Part 1) or 18 months (Part 2). The Part 1 and Part 2 studies will have independently randomized, unique study populations.

The Part 1, 6-month, double-blind treatment portion of the study will include 5 clinic visits. The primary objective of the Part 1 portion is to evaluate the efficacy of 6 months of oral azeliragon on a measure of cognition (ADAS-cog14). Secondary objectives of Part 1 will be to evaluate the efficacy of 6 months of oral azeliragon on multiple measures of function to inform selection of a functional endpoint to serve as co-primary in Part 2, as well as the sample size required to adequately power the study to detect treatment effect on cognitive and functional measures in the study population. Upon completion of Part 1, a subject's participation is considered complete and they will not be permitted to participate in Part 2. The Schedule of Activities for Part 1 is described in Table 1.

The Part 2, 18-month, double-blind treatment portion of the study will include 9 clinic visits. Part 2 will enroll 200 subjects who will be randomized to receive oral azeliragon 5 mg/day or placebo in a 1:1 randomization. The Schedule of Activities for Part 2 is described in Table 2.

A minimum of three staff members will be required to conduct the protocol at each site.

- Principal Investigator (PI) – This person is responsible for the clinical evaluation of all participants, ensuring subject eligibility, enrollment and protocol adherence, endpoint determinations, and medical decisions related to the study. The PI will supervise project personnel and ensure that raters maintain a high level of skill and accuracy in conducting assessments. The PI may not serve as the CDR Rater.

- Study Coordinator – This person will be responsible for managing day-to-day conduct of the trial, track recruitment, and ensure accurate administration of all instruments at the site, supervise data collection, processing of laboratory samples, and maintain a log of treatment adherence. The study coordinator may serve as a rater. If s/he is responsible for study oversight and other study assessments, s/he may not serve as the CDR Rater.

- Non-CDR Rater – This person will meet the education, clinical and scale experience requirements set by the sponsor. This person can conduct all ratings and assessments, once qualified by the rater training staff, except for the CDR. If appropriately qualified, the PI or Study Coordinator may also fulfill this role.

- CDR Rater – This person will render the CDR rating based on clinical assessment of participant and caregiver / study partner, using scale worksheets provided by the Sponsor, but without access to the ADAS-cog or any other study assessments, including adverse events and laboratory data. Neither the PI nor the Study Coordinator responsible for study oversight may fulfill this role.

4.0 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

Subject eligibility must be reviewed and documented by an appropriately qualified member of the Principal Investigator's (PI's) study team before participants are included in the study.

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally authorized representative) and caregiver/informant has been informed of all pertinent aspects of the study. Participants must be able to provide consent or assent (where this is in accordance with local laws, regulations and ethics committee policy) and consent/assent must be re-evaluated during the study at regular intervals.

2. Male or female subjects aged 50-85 years (inclusive) at Screening Visit.

3. Female subjects must be of non-childbearing potential. Male subjects with female partners of child bearing potential must agree to acceptable birth control for the duration of the study and for 90 days thereafter.

4. If on pharmacological treatment for diabetes, must be on stable dose for at least 60 days prior to screening and remain stable through Baseline. There should be expectation that treatment and dose will remain stable during the study period.

5. Clinical diagnosis of probable Alzheimer's disease, consistent with the criteria from the 2011 National Institute on Aging and Alzheimer's Association workgroup [McKhann 2011], for at least 2 months prior to Screening. Evidence of progression must be documented in source documentation at the time of screening based on review of prior medical records and/or information gathered from the subject or caregiver/informant(s).

6. Mini-Mental State Exam (MMSE) score of 21-26 inclusive at Screening and 19-27 at Baseline.

7. CDR global score of 0.5 or 1 at Screening and Baseline.

8. ADAS-cog14 score of ≥10 at Screening and Baseline.

9. Participant must be on a stable dose of a background cholinesterase inhibitor and/or memantine (approved by relevant health authority where trial is being conducted) at least 60 days prior to Screening and remain stable through Baseline. There must be agreement not to change the treatment or dose during the study period unless the investigator judges that the dose needs to be reduced or stopped due to a safety and/or tolerability reason.

10. Hemoglobin A1c (HbA1c) 6.5% - 9.5%, inclusive, at Screening.

11. Body mass index (BMI) 19.0 – 37.0 kg/m2, inclusive, at Screening Visit and Baseline Visit.

12. Body weight at least 45.0 kg at Screening Visit and Baseline Visit.

13. Participants and caregiver/informants who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

14. The subject must have a reliable caregiver/informant with regular contact (i.e., 10 hours a week as combination of face-to-face visits and telephone contact acceptable) who will facilitate the subject's full participation in the study. Caregiver/informant must have sufficient subject interaction to be able to provide meaningful input into the rating scales administered in this study where caregiver/informant input is required, and evidence of this should be documented in source documentation. Participants who reside in assisted living facilities are permitted provided that they meet caregiver/informant criteria.

15. Participants and caregiver/informants must be able to read, write, and speak the language in which psychometric tests are provided with visual and auditory acuity (corrected) sufficient to allow for accurate psychometric testing.

16. Subject must be able to ingest oral medications.

4.2 EXCLUSION CRITERIA

Participants presenting with any of the following will be excluded from participation in the study.

1. Current evidence or history of neurological or any other illness that could contribute to dementia including, but not limited to, other neurocognitive

disorders (e.g., Lewy body disease, fronto-temporal dementia, Parkinson disease), HIV cognitive impairment, head injury with loss of consciousness proximate to the onset of dementia, vitamin B12 deficiency (see Exclusion 3, below) or thyroid disease (unless adequately treated for at least 3 months with normalization of laboratory values).

2. Participants from a family with known autosomal dominant AD associated with mutations in APP, PS1 or PS2 genes or strongly suspected, but not yet identified mutations in APP, PS1 or PS2 genes, or Down's syndrome. Individuals from families with any number of late onset AD affected family members may participate in this study.

3. Vitamin B12 levels lower than laboratory reported normal limits (and remains below on repeat testing). Participants may be enrolled following the initiation of B12 therapy for 4 weeks prior to dosing and confirmed within normal limits upon repeat.

4. Evidence of neurologic deficits from a previous stroke or MRI changes consistent with multi-infarct dementia. Diagnosis or any history of cerebrovascular stroke, severe carotid stenosis, cerebral hemorrhage, intracranial tumor, subarachnoid hemorrhage that, as determined by the investigator, could either contribute to the patient's current cognitive or functional status, impair his/her ability to fully participate in the trial or that may impact his/her status during the course of the trial.

5. Specific exclusionary brain MRI findings (as identified on the central MRI read) as determined by the investigator that could either significantly contribute to the patient's current cognitive or functional decline, impair his/her ability to fully participate in the trial or that may impact his/her status during the course of the trial. In any case, the following are exclusionary:

   a) 10 or more microhemorrhages as identified by the central reading report.

   b) Grade three deep white matter changes (diffuse involvement of entire region) on the central reading report.

6. History of schizophrenia or late onset (after age 40) bipolar disorder. Current or recent (within 6 months prior to Screening) clinically relevant or unstable psychiatric disorder (e.g., major depressive disorder) that, per the investigator's

judgment, could significantly contribute to the patient's current cognitive or functional decline, impair his/her ability to fully participate in the trial, or may impact his/her status during the course of the trial.

7. Serious suicide risk per the following criteria:
   a) Suicidal ideation associated with intent and/or plan within the previous year as indicated by a "yes" answer on Items 4 or 5 of the C-SSRS;
   b) History of suicidal behavior within the previous 10 years as indicated by a "yes" answer to any of the suicidal behavior items of the C-SSRS with a behavior occurring within the previous 10 years;
   c) Lifetime history of serious or recurrent suicidal behavior (serious is defined as actual lethality/medical damage score > 2 on Screening C-SSRS)
8. History of cancer within the last 5 years except adequately treated cervical carcinoma in-situ, cutaneous basal cell or squamous cell cancer, or non-progressive prostate cancer not requiring current treatment.
9. Participants with poorly controlled hypertension with or without existing therapy (ex: systolic≥140 mmHg or diastolic ≥90 mmHg with repeated measures) at Screening or Baseline. Subjects with repeated measures of systolic≥140 mmHg or diastolic ≥90 mmHg at Screening will be allowed to participate with management of blood pressure below the exclusionary levels with introduction of an allowable medication and the subject has been on the drug for 4 weeks prior to Baseline. Subjects with repeated measures of systolic≥140 mmHg or diastolic ≥90 mmHg at Baseline will be excluded.
10. Participants with evidence or history of severe drug allergies (such as resulting in dyspnea or severe rash) or allergy to any constituents of the study drug as formulated.
11. Known history or current evidence of moderate to severe substance use disorder according to DSM-5 criteria within 1 year prior to Screening or a positive result on the drug screening test (unless due to a permitted concomitant medication [e.g., a benzodiazepine as a sleep aid]).
12. Subjects with pulmonary hypertension are excluded.

13. Previous participation and dosing in another clinical trial for Alzheimer's disease as follows:

    a. Exposure to putative disease modifying therapies within 1 year before Screening Visit is exclusionary, unless placebo treatment assignment is documented.

    b. Exposure to symptomatic therapy within 90 days (or five half-lives, whichever is longer) before Screening Visit is exclusionary.

    Any clinical trial (Alzheimer's or non-Alzheimer's) study visit within 90 days before the Screening Visit is exclusionary regardless of treatment assignment.

14. Participants who are taking or are expected to use drugs known to be strong CYP2C8 inhibitors.

15. Participants receiving systemic steroids. Topical corticosteroid application to the skin is allowed, as are localized corticosteroid injections if administered no more than once every 6 months during the last year and are expected to be administered no more frequently during the study. Use of inhaled, intranasal or otic steroids are not excluded.

16. Participants receiving medications that may negatively affect cognitive function (e.g., antidepressants, antipsychotics, sedatives/anxiolytics) unless such medications have been taken at a stable dose for at least 4 weeks prior to enrollment (i.e., in the investigator's judgment, efficacy and tolerability have been optimized) and are expected to continue on a stable dose for the duration of the trial.

17. Prescription medical food (i.e., Axona) intended for the dietary management of the metabolic processes associated with Alzheimer's disease.

18. Participants may not donate blood within 8 weeks prior to enrollment and for 6 months after the last administration of study drug.

19. History of clinically significant or current unstable cardiac disease as determined by the PI and in consultation with the Sponsor. Examples of cardiac disease that would be exclusionary include 2nd degree or greater heart block without a pacemaker, sick sinus syndrome, ventricular tachycardia or fibrillation, sustained supraventricular tachycardia, symptomatic bradycardia, congenital long QT interval syndrome, atrial fibrillation, clinically significant

angina/coronary artery disease, myocardial infarction in the past year, congestive heart failure, cardiomyopathy, myocarditis, left ventricular hypertrophy, valvular heart disease requiring treatment or life style modification. Subjects with atrial fibrillation on anticoagulant therapy and who have had no thromboembolic events or other referable cardiac events in the preceding 1 year are considered stable and may be screened.

20. Participants demonstrating QTcF > 470 msec on Screening 12-lead ECG (confirmed with a repeat measure). Participants with known history of bundle branch block (either right or left) are allowed if QTcF value does not exceed 500 msec. Participants with a functioning pacemaker, indicated by an ECG displaying paced rhythm, are allowed with no QTcF upper limit.

21. History of diabetic ketoacidosis within the last year.

22. History of more than one severe episode of hypoglycemia that required assistance by a third party within the past year.

23. History of chronic pancreatitis.

24. Current clinically significant hepatic disease or elevated LFTs ≥ 2 times the upper limit of normal (ULN) at Screening.

25. Stage 4 kidney disease (estimated GFR < 30 mL/min/1.73 m^2, as calculated by the CKD-EPI equation [Levey 2009]).

26. Any laboratory value not already specified above that is outside the laboratory reference range and considered by the Principal Investigator, or appropriately qualified designee, to be a clinically significant abnormality.

27. Use of insulin therapy.

28. Any other medical condition or reason that, in the opinion of the Principal Investigator or appropriately qualified designee, makes the subject unsuitable to participate in this clinical trial.

Eligibility for randomization will be reviewed and approved by an independent Randomization Authorization Committee. The remit of this committee will be to ensure each patient deemed by the Investigator to be eligible for the trial meets key eligibility criteria and is suitable for participation in the study.

4.3 CONTRACEPTION REQUIREMENTS AND STUDY PARTICIPANT INSTRUCTION

4.3.1 Males

A fertile male study participant, whose sexual partner is female and of childbearing potential, must agree to use one of the following methods of contraception for the duration of the study (from the first dose until 90 days after the final dose of the study medication): abstinence, use of condom plus their female partners must use another form of contraception including implants, injectables, combined oral contraceptives, barrier contraception methods, spermicides, intrauterine devices (IUDs), transdermal contraceptives, and intravaginal contraception rings. The male study participant should also agree to no sperm donation for 90 days after the final dose of study medication.

At appropriate study visits, all study participants are reminded of contraception requirements as described above. Upon discharge from the study, subjects will be instructed to notify the Study Site if a female study participant or female partner of a male study participant becomes pregnant within 90 days of last dose of study medication.

4.3.2 Females

Only females of non-child bearing potential are allowed in the study. Screening laboratory FSH values will be obtained on all females to confirm post-menopausal status for those females who are not surgically sterile. No additional birth control is required.

5.0 STUDY TREATMENTS

5.1 PROCESS FOR RANDOMIZATION TO STUDY TREATMENT

Subjects will be screened by Investigators or qualified designees to assess eligibility for randomization into the study. An interactive voice response system (IVRS)/ interactive web response system (IWRS) will be used for assignment of treatment.

Subjects will be enrolled and randomized according to a fixed randomization scheme blocked by study investigative site. Randomization will have balanced allocation (1:1) between azeliragon and placebo. Dropouts will not be replaced.

5.2 PROCESS FOR EMERGENCY BREAKING THE BLIND

The study will be double-blind. At the initiation of the study, the study site will be instructed on the electronic process for breaking the blind. Blinding should only be broken in emergency situations when knowledge of the treatment assignments is necessary for subject safety. Upon breaking the blind, the reason must be documented in the electronic data capture system. The sponsor or representative should be consulted prior to breaking the blind except in emergent circumstances.

5.3 DRUG SUPPLIES

Drug supplies will consist of a 5 mg and matching placebo formulation supplied as a Size 2 hard gelatin capsule in a double-blind fashion. The recommended storage condition for the product is room temperature at 15ºC to 30ºC (59ºF to 86ºF).

5.3.1 Formulation and Packaging

Azeliragon and matching placebo capsules will be packaged into child-resistant, high density polyethylene (HDPE) bottles with heat induction seal (HIS) closures. Supplies will be packaged in a blinded fashion. All doses and formulations are identical in appearance and packaging.

Storage conditions and participant dosing instructions will be listed on the packaging.

5.3.2 Administration

Treatment will begin in the clinic at the baseline visit immediately following randomization. One capsule will be administered with a glass of water. Participants will be instructed to take one capsule per day by mouth for the duration of the treatment period. The day's dose of study medication will be administered in the clinic at the end of each subsequent study visit. Study medication may be administered without regard to meals.

5.3.3 Compliance

Participants will bring all unused azeliragon/placebo capsules to each study visit. The number of capsules will be counted and documented. If more than expected are returned, participants will be asked to account for missed doses. If the number of capsules is less than expected, participants will be asked to account for the missing capsules (e.g., capsules that are lost vs. excessive dosing of study medication). Caregivers/Informants will be instructed to assist with monitoring dosing compliance. Dosing compliance < 90% or > 100% for a 3-month period will be documented as a protocol deviation.

5.3.4 Drug Storage and Drug Accountability

Study drug supplies must be stored at room temperature (15°C –30°C [59°F-86°F]) in a secure and locked area. The pharmacist or designee at the study site will manage and store the study drug.

Study drugs will be accounted for in the case report form and drug accountability inventory forms as instructed by the Sponsor. At the end of the study, all drug supplies not dispensed or unused by the participants must be returned to the location designated by the Sponsor.

5.4 CONCOMITANT MEDICATION(S)

All participants will be questioned about concomitant medication and supplements at each study visit. Concomitant medications (including over the counter medications and supplements) taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. During the study,

participants should be instructed to review new prescriptions and over-the-counter preparations with the investigator prior to taking any medications. All new medications should be discussed with the investigator and recorded on the Case Report Form (CRF). If the medication is started because of an adverse event (AE) or medical history indication, this event should be reported on the appropriate CRF.

- Medications taken within 60 days prior to screening must be documented as a prior medication.
- All past medications/therapies for dementia, regardless of timing relative to screening, must be recorded.
- Medications taken after the first dose of study medication must be documented as concomitant medications.

The following are specific considerations with regard to use of concomitant medications. Any additional questions regarding medications should be addressed to the Sponsor's medical monitor.

Anti-diabetic therapy:

- Participants on anti-diabetic therapy must be on a stable dose for at least 60 days prior to Screening and remain stable through Baseline. There should be expectation that treatment and dose will remain stable for the duration of the trial.
- Participants using insulin therapy are excluded from study participation.

Treatment for dementia:

- All participants must be on a stable dose of background therapy (cholinesterase inhibitor and/or memantine) at least 60 days prior to Screening and remain stable through Baseline. There must be agreement to continue at the stable treatment and dose for the duration of the trial.
- Dose reductions of background therapy are permitted during the course of the trial (e.g., due to safety/tolerability or to conform with local standard of care).

- Dose increases of background cholinesterase inhibitor and/or memantine during the course of the trial will be considered major protocol deviations.

Medications that may affect behavior or cognitive function (e.g., antidepressants, antipsychotics, sedatives/anxiolytics) must be at a stable dose (i.e., in the investigators judgment, efficacy and tolerability have been optimized) for at least 4 weeks prior to randomization and are expected to continue on a stable dose for the duration of the trial. (Dose adjustments are permitted however participants must be on a stable dose at least one week prior to any protocol-specified clinical assessments). Exceptions to medications that may negatively affect cognitive function are as follows:

- Participants may receive pre-medication (e.g., sedative or anxiolytic) for the MRI or CT scan assessment. This medication should not be administered within 5 half-lives preceding any efficacy assessments.

- Considerations for use of medications that may affect the CNS or cognition following randomization. Generally, medications that affect cognition are not allowed. In such case that there is an acute need for use of a medication that may negatively affect cognition or the CNS in general (e.g., sedatives/anxiolytics, antipsychotics, opiates), their use should be transient (no more than 4 weeks), must be stable for at least one week prior to any cognitive assessments, and discussed with the sponsor's medical monitor prior to use (or as soon as possible following discovery of their use). Chronic use of these medications is not permitted. Should their use be deemed to be chronic (spanning months), discussion with the Sponsor's medical monitor is required regarding continued participation in the trial.

The use of following concomitant medications is not allowed:

- Drugs known to be strong CYP2C8 inhibitors (See APPENDIX 2 for a list).

- Any use of steroid treatment. Allowable exceptions: a) topical, otic, nasal or inhaled corticosteroid applications to the skin, and b) localized corticosteroid injections, no more than once every 6 months.

- Prescription medical food (i.e. Axona) intended for the dietary management of the metabolic processes associated with Alzheimer's disease.

- No investigational therapies for any indication within 30 days or 5 half-lives (whichever is longer) before Screening Visit, will be permitted. Also, no investigational therapies for any indication will be permitted during study participation.

- Insulin therapy

6.0 STUDY PROCEDURES

- Study participants must arrive at clinic visits following an overnight (8 hour) fast to collect clinical lab samples in a fasted state. A separate clinic visit within the protocol-allowed visit window may also be utilized for collecting fasting clinical lab samples.

- Anti-diabetic medication, if normally taken in the morning, should be withheld the morning of clinic visits and taken at the same time as the meal or snack.

- Following fasted blood sampling, the subject must consume a low carbohydrate / high protein meal or snack prior to the rest of the study procedures, if performed on the same day. The time of finishing the meal/snack must be documented in the source documents.

- An on-site point of care blood glucose measurement must be obtained prior to neuropsychological assessments and documented in the source documents.
  - If subject is hypoglycemic (<90mg/dL), feed the subject (again) and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.

- Cognitive/functional assessments must be performed following the meal/snack and blood glucose measurement, during a study visit.

- It is required that cognitive/functional assessments be performed with the subject in the following order: MMSE, ADAS-cog, patient portion of the CDR when administered on the same day. The same rater should follow a particular subject for any given assessment for the duration of the study whenever possible.

- Dosing should occur in the clinic on study visit days from the newly dispensed study medication supply. If the subject has already dosed with study drug on the clinic day, they should not be dosed in the clinic. The study drug will be dispensed and the subject instructed to dose at home the following day

according to their usual schedule. This will be documented in source documents and be listed as a minor protocol deviation.

6.1 SCREENING / Part 1 and Part 2

For logistical purposes, up to 60 days will be allowed for screening to confirm that participants meet all selection criteria for the study. It is strongly encouraged that the screening period is minimized to the shortest possible duration whenever possible. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject, caregiver/informant, and when appropriate, legally authorized representative in accordance with Subject Information and Informed Consent/Assent (where this is in accordance with local laws, regulations and ethics committee policy). The screening assessments may be separated out into more than one visit if required. Refer to the Schedule of Events for a tabular presentation for screening activities (Table 1, Table 2).

The following activities will be completed:

- Complete informed consent/assent process (where this is in accordance with local laws, regulations and ethics committee policy) resulting in a signed ICF(s) by the appropriate parties.
- Assign screening identification number.
- Fasting blood and urine specimens for safety laboratory tests (serum chemistry, hematology, UA) will be collected, in addition to the following:
  - Plasma glucose and HbA1c
  - Hepatitis screens (including hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, and hepatitis C antibody)
  - Thyroid function (T3, T4, and TSH)
  - Vitamin B12
  - Serum FSH concentrations in all female participants to confirm post-menopausal status and eligibility regarding non-child bearing potential
  - Urine drug screen

- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE.
- ADAS-cog14.
- CDR (calculation of both global score and sum of boxes score).
- Columbia Suicide Severity Scale (C-SSRS).
- Demographic information (i.e., sex, date of birth, race/ethnicity).
- Complete medical and surgical history, including family medical history of dementia.
- History of prior participation and dosing in a clinical trial.
- Record and review all prior medications for Alzheimer's disease.
- Record and review concomitant medications and any discontinued medication in the 60 days prior to the Screening visit.
- History of drug, alcohol and tobacco use.
- Complete physical and neurological exams.
- Height, body weight, and body mass index (BMI) calculation.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Single 12-lead electrocardiogram (ECG) after 5 minutes rest. Repeat ECG if QTcF > 470 msec.

- Review of inclusion and exclusion criteria.

- Brain MRI should be performed at least 14 days prior to Month 0/Day 1 dosing to allow time for central read; the MRI may also include gadolinium contrast if determined to be appropriate by the investigator. For subjects with a contraindication to MRI scanning (e.g. pacemaker), a CT scan will fulfill the requirements for assessing subject eligibility. Use of contrast is allowed upon investigator discretion.

Re-screening of a Participant

Participants who had been screened and failed to join the study based on the following reasons are allowed to re-screen if the subject is beyond the original 60-day screening window. A re-screening subject must receive a new screening ID.

Participants do not have to repeat the MRI if dosing occurs within 90 days from the initial screening MRI.

- Participants with Vitamin B12 below the normal limits at initial screening.

- Participants must subsequently have been taking Vitamin B12 for at least 4 weeks after initial screen failure and have repeat B12 level within the normal range.

- Participants who are not on a stable dose of anti-diabetic therapy for at least 60 days prior to Screening may rescreen once they have reached at least 60 days of stable dosing.

- Participants who are not on a stable dose of dementia therapy for at least 60 days prior to Screening may rescreen once they have reached at least 60 days of stable dosing.

- Hypertension discovered at screening that is subsequently actively managed and the blood pressure values are within acceptable limits.

- Subjects who have a Screening CDR global of 0 or an MMSE score >26 may rescreen upon approval of the sponsor's medical monitor. Screening CDR global scores greater than 1 or MMSE scores less than 21 may not rescreen.

The time to rescreen a subject is up to the investigator but in any case, may not be within 3 months with no upper time limit. They may rescreen only once. Subjects who score out of range are considered a screen fail, even if they are planning to rescreen.

- Subjects who did not complete the screening procedures within the protocol-specified 60-day window may rescreen.
- Subjects who have a Screening HbA1c outside of the eligible range may re-test HbA1c during the screening period and re-assess eligibility. If the 60-day Screening period elapses, the subject may re-screen with a new Screening ID

6.2 PART 1 STUDY PERIOD

6.2.1 Part 1 / Baseline (approximately Day -7-Day 1)

- Assessment of continued consent / assent (where applicable).
- Fasting clinical laboratories:
  - Collect blood sample for plasma retention and storage.
  - Blood sample for ApoE genotyping.
  - Blood and urine sampling for safety labs including HbA1c.
  - Collect blood samples for PK and PD.
- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14, CDR, FAQ, Amsterdam-IADL.
- C-SSRS.

- Brief physical and neurologic examination.
- Update concomitant medications.
- Body weight.
- Assess baseline symptoms/adverse events.
- 12-lead electrocardiogram (ECG) after 5 minutes rest. Perform triplicate measures and use the average QTcF for inclusion.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest. Perform triplicate measures and use the average blood pressure readings for inclusion.
- Review of inclusion and exclusion criteria including the results of Screening laboratories and Screening MRI scan, and confirm continued eligibility

Day 1

At the conclusion of the Baseline visit, the following procedures are performed if the subject is confirmed eligible:

- Randomize subject if eligible.
- Dispense study drug if eligible.
- Subject takes first dose of study medication in the clinic under observation and time of dosing recorded.

If the baseline assessments are performed on more than one day, up to 7 days are allowed for completion of baseline procedures prior to subject randomization and dosing. The 7-day window will begin on the day that the first baseline assessment is performed and ends on the day when the subject is randomized, and study drug is administered.

If it is necessary to extend the 7-day period for any other reason (e.g., schedule conflicts, patient/caregiver/informant illness, inclement weather) the Sponsor should be contacted for approval and the visit window may be extended up to 7 days. In this case, re-review of the inclusion/exclusion criteria and concomitant medications should occur within 7 days prior to the first dose to ensure that the patient continues

to be appropriate for the study. Other baseline procedures may be repeated at the discretion of the Investigator but are not required. The 60-day period from screening to first dose remains in effect. Should the overall screening time exceed 60 days, re-screening is required.

6.2.2 Part 1 / Month 1 Telephone Contact (Day 30 ± 7 days)

- Telephone contact with subject and caregiver (separate or combined).
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Assess drug compliance with the question "Have you been taking your medication every day as instructed?"

6.2.3 Part 1 / Month 2 Telephone Contact (Day 60± 7 days)

- Telephone contact with subject and caregiver (separate or combined).
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Assess drug compliance with the question "Have you been taking your medication every day as instructed?"
- Provide subject and caregiver with instructions for next visit (e.g., date, requirement for fasting blood samples, hold dosing on morning of visit, return used study drug bottles).

6.2.4 Part 1 / Month 3 Clinic Visit (Day 90 ± 7 days)

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.

- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam-IADL.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as “How have you been feeling?”
- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Return study drug.
- Drug accountability. Any discrepancies are recorded in the source and the subject and caregiver/informant are counseled regarding proper dosing compliance.
- Dispense study drug.
- Subjects take their daily dose of study medication in the clinic.

6.2.5 Part 1 / Month 4 Telephone Contact (Day 120 ± 7 days)

- Telephone contact with subject and caregiver (separate or combined).
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as “How have you been feeling?”
- Assess drug compliance with the question “Have you been taking your medication every day as instructed?”

6.2.6 Part 1 / Month 5 Telephone Contact (Day 150 ± 7 days)

- Telephone contact with subject and caregiver (separate or combined).
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as “How have you been feeling?”
- Assess drug compliance with the question “Have you been taking your medication every day as instructed?”
- Provide subject and caregiver with instructions for next visit (e.g., date, requirement for fasting blood samples, hold dosing on morning of visit, return used study drug bottles).

6.2.7 Part 1 / Month 6 Clinic Visit (Day 180 ± 7 days)

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.
- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.

- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam-IADL.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Return study drug.
- Drug accountability. Any discrepancies are recorded in the source.

6.2.8 Part 1 / Follow-Up Visit

A Follow-up Visit will be completed 3 months [90 ± 7 days] after a subject completes Month 6 for those participants who complete the study; or at least 45 days after the last dose of study drug, if the subject discontinues the study prior to Month 6.

If a subject does not complete a follow up visit, the reason and efforts to contact subjects for follow-up should be documented in the source and EDC. An Early Termination Visit does not satisfy the requirements for a Follow-Up Visit.

At any point, if a participant withdraws consent, no further evaluations should be performed, and no additional data should be collected.

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.
- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam-IADL.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as “How have you been feeling?”
- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.

6.2.9 Part 1 / Early Termination

In the event a subject discontinues participation prior to completion of the Month 6 Visit and less than 45 days have elapsed since the subject's last dose of study drug, the Early Termination Visit should be completed, performing the study procedures as follows. In all cases, a Follow-up Visit (as described in Section 6.2.8) should be performed approximately 3 months after the last dose of study drug. However, if a participant withdraws consent prior to early termination, no further evaluations should be performed, and no additional data should be collected.

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.
- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam-IADL.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Brief physical and neurologic examination.
- Body weight.

- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Return study drug.
- Drug accountability. Any discrepancies are recorded in the source.

6.3 PART 2 STUDY PERIOD

6.3.1 Part 2 / Baseline (approximately Day -7-Day 1)

- Assessment of continued consent / assent (where applicable).
- Fasting clinical laboratories:
  - Collect blood sample for plasma retention and storage.
  - Blood sample for ApoE genotyping.
  - Blood and urine sampling for safety labs, including HbA1c.
  - Collect blood samples for PK and PD.
- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14, CDR, FAQ, Amsterdam-IADL, NPI, DEMQOL-proxy.
- C-SSRS.
- Brief physical and neurologic examination.
- Update concomitant medications.

- Body weight.
- Assess baseline symptoms/adverse events.
- 12-lead electrocardiogram (ECG) after 5 minutes rest. Perform triplicate measures and use the average QTcF for inclusion.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest. Perform triplicate measures and use the average blood pressure readings for inclusion.
- Review of inclusion and exclusion criteria including the results of Screening laboratories and Screening MRI scan, and confirm continued eligibility.

Day 1

At the conclusion of the Baseline visit, the following procedures are performed if the subject is confirmed eligible:

- Randomize subject if eligible.
- Dispense study drug if eligible.
- Subject takes first dose of study medication in the clinic under observation with time of dosing recorded.

If the baseline assessments are performed on more than one day, up to 7 days are allowed for completion of baseline procedures prior to subject randomization and dosing. The 7-day window will begin on the day that the first baseline assessment is performed and ends on the day when the subject is randomized, and study drug is administered.

If it is necessary to extend the 7-day period for any other reason (e.g., schedule conflicts, patient/caregiver/informant illness, inclement weather) the Sponsor should be contacted for approval and the visit window may be extended up to 7 days. In this case, re-review of the inclusion/exclusion criteria and concomitant medications should occur within 7 days prior to the first dose to ensure that the patient continues to be appropriate for the study. Other baseline procedures may be repeated at the discretion of the Investigator but are not required. The 60-day period from screening to first dose remains in effect. Should the overall screening time exceed 60 days, re-screening is required.

6.3.2 Part 2 / Month 1 Telephone Contact (Day 30 ± 7 days)

- Telephone contact with subject and caregiver (separate or combined).
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Assess drug compliance with the question "Have you been taking your medication every day as instructed?"

6.3.3 Part 2 / Month 2 Telephone Contact (Day 60 ± 7 days)

- Telephone contact with subject and caregiver (separate or combined).
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Assess drug compliance with the question "Have you been taking your medication every day as instructed?"
- Provide subject and caregiver with instructions for next visit (e.g., date, requirement for fasting blood samples, hold dosing on morning of visit, return used study drug bottles).

6.3.4 Part 2 / Month 3 Clinic Visit (Day 90 ± 7 days)

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.
- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.

- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam-IADL, NPI, DEMQOL-proxy.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Return study drug
- Drug accountability. Any discrepancies are recorded in the source and the subject and caregiver/informant are counseled regarding proper dosing compliance.
- Dispense study drug. Subjects take their daily dose of study medication in the clinic.
- Provide subject and caregiver with instructions for next visit (e.g., date, requirement for fasting blood samples, hold dosing on morning of visit, return used study drug bottles).

6.3.5 Part 2 / Month 6 Clinic Visit (Day 180 ± 7 days)

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.
- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam-IADL, NPI, DEMQOL-proxy.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as “How have you been feeling?”
- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Return study drug.

- Drug accountability. Any discrepancies are recorded in the source and the subject and caregiver/informant are counseled regarding proper dosing compliance.

- Dispense study drug. Subjects take their daily dose of study medication in the clinic.

- Provide subject and caregiver with instructions for next visit (e.g., date, requirement for fasting blood samples, hold dosing on morning of visit, return used study drug bottles).

6.3.6 Part 2 / Month 9 Clinic Visit (Day 270 ± 7 days)

- Assessment of continued consent / assent (where applicable).

- Fasting blood and urine sampling for safety labs, including HbA1c.

- Collect blood sample for plasma retention and storage.

- Collect blood samples for PK and PD.

- Provide subject with a meal/snack.

- Check blood sugar, using point of care device, after an appropriate time.

  – If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.

  – If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.

- MMSE, ADAS-cog14.

- C-SSRS.

- Review and record new concomitant medications.

- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as “How have you been feeling?”

- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Return study drug.
- Drug accountability. Any discrepancies are recorded in the source and the subject and caregiver/informant are counseled regarding proper dosing compliance.
- Dispense study drug. Subjects take their daily dose of study medication in the clinic.
- Provide subject and caregiver with instructions for next visit (e.g., date, requirement for fasting blood samples, hold dosing on morning of visit, return used study drug bottles).

6.3.7 Part 2/ Month 12 Clinic Visit (Day 360 ± 7 days)

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.
- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.

- MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam-IADL, NPI, DEMQOL-proxy.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Return study drug.
- Drug accountability. Any discrepancies are recorded in the source and the subject and caregiver/informant are counseled regarding proper dosing compliance.
- Dispense study drug. Subjects take their daily dose of study medication in the clinic.
- Provide subject and caregiver with instructions for next visit (e.g., date, requirement for fasting blood samples, hold dosing on morning of visit, return used study drug bottles).

6.3.8 Part 2 / Month 15 Clinic Visit (Day 450 ± 7 days)

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.
- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.

- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Return study drug.
- Drug accountability. Any discrepancies are recorded in the source and the subject and caregiver/informant are counseled regarding proper dosing compliance.
- Dispense study drug. Subjects take their daily dose of study medication in the clinic.
- Provide subject and caregiver with instructions for next visit (e.g., date, requirement for fasting blood samples, hold dosing on morning of visit, return used study drug bottles).

6.3.9 Part 2 / Month 18 Clinic Visit (Day 540 ± 7 days)

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.
- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam-IADL, NPI, DEMQOL-proxy.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as “How have you been feeling?”
- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Return study drug.
- Drug accountability. Any discrepancies are recorded in the source.

- Brain MRI. For subjects with a contraindication to MRI scanning (e.g., pacemaker), no brain MRI is required for this visit.

6.3.10 Part 2 / Follow-Up Visit

A Follow-up Visit will be completed 3 months [90 ± 7 days] after a subject completes Month 18 for those participants who complete the study; or at least 45 days after the last dose of study drug if the subject discontinues the study prior to Month 18.

If a subject does not complete a follow up visit, the reason should be documented in the source and EDC. An Early Termination visit does not satisfy the requirement for a Follow-Up Visit.

At any point, if a participant withdraws consent, no further evaluations should be performed, and no additional data should be collected.

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.
- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.
  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.
- MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam-IADL, NPI, DEMQOL-proxy.
- C-SSRS.

- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.

6.3.11 Part 2 / Early Termination

In the event a subject discontinues participation prior to completion of the Month 18 Visit and less than 45 days have elapsed since the subject's last dose of study drug, the Early Termination Visit should be completed performing the study procedures as follows. In all cases, a Follow-up Visit (as described in Section 6.3.10) should be performed approximately 3 months after the last dose of study drug. However, if a participant withdraws consent prior to early termination, no further evaluations should be performed, and no additional data should be collected.

- Assessment of continued consent / assent (where applicable).
- Fasting blood and urine sampling for safety labs, including HbA1c.
- Collect blood sample for plasma retention and storage.
- Collect blood samples for PK and PD.
- Provide subject with a meal/snack.
- Check blood sugar, using point of care device, after an appropriate time.
  - If subject is hypoglycemic (<90mg/dL), feed the subject again and re-check blood sugar prior to neuropsychological assessments.

  - If subject is hyperglycemic (>300mg/dL), reschedule the neuropsychological assessments for a proximal day within the visit window.

- MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam-IADL, NPI, DEMQOL-proxy.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events by asking the participants to respond to a non-leading question such as "How have you been feeling?"
- Brief physical and neurologic examination.
- Body weight.
- 12-lead electrocardiogram (ECG) after 5 minutes rest.
- Vital signs: blood pressure (supine), pulse rate after 5 minutes rest.
- Return study drug.
- Drug accountability. Any discrepancies are recorded in the source.
- Brain MRI. For subjects with a contraindication to MRI scanning (e.g., pacemaker), no brain MRI is required for this visit.

6.4 SUBJECT WITHDRAWAL

Participants may withdraw from the study at any time at their own request or the request of their study partner, caregiver/informant/guardian, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, compliance, or administrative reasons. If a participant does not return for a scheduled visit, every effort should be made to contact the participant including certified letter, return receipt requested. The investigator should inquire about the reason for withdrawal, request that the participant return all unused investigational product(s), request that the participant return for any remaining clinic visits.

If the participant withdraws from the study and joins another clinical study or does not wish to complete the remaining clinic visits, an Early Termination and/or Follow-up Visit should be performed as follows:

- An Early Termination should be performed if less than 45 days have elapsed since the subject's last dose of study drug.
- A Follow-up Visit should be performed when ≥ 45 days have elapsed since the subject's last dose of study drug.

Continued follow-up with the participant may be required if there are any unresolved adverse events (refer to Section 8.7).

If the participant withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. An individual patient enrolled in the trial may be discontinued from dosing (and continue in the study) based on a specific adverse event profile as recommended by either the IDMC and/or the Sponsor in discussions with the PI. The IDMC or the Sponsor may temporarily stop dosing of enrolled subjects and/or additional enrollment of new patients at any time and may permanently terminate the study at any time.

Any emergent medical condition or safety finding that, in the opinion of the Investigator, may jeopardize the participant's safety if he/she continues dosing will be sufficient reason to discontinue dosing (temporarily or permanently), while the participant continues in the study. The participant should be followed as indicated for the AE until resolved, declared stable or the participant is lost to follow up. Safety data will be obtained from the physical and neurological examination, vital signs, routine laboratory tests, ECG, and neuropsychological testing batteries. Once resolved, the Investigator and Medical Monitor may discuss if it would be appropriate to re-start dosing.

7.0 ASSESSMENTS

7.1 SAFETY AND TOLERABILITY

7.1.1 Body Measurements

Height (cm) will be measured at the Screening Visit, without shoes.

Body weight (kg) will be measured on the same scale without shoes, coats, or sweaters.

BMI will be calculated as body weight (kg) / height (m) ^{2}.

7.1.2 Vital Signs

Vital signs measurements will consist of blood pressure and pulse rate while the participant is supine. Vital signs will be conducted at all the study visits. Participant should have been supine at least 5 minutes prior to vital signs determination. At Baseline, pre-dose measurements will be performed in triplicate; all other vital signs readings (at time points shown in the Schedule of Activities) will be a single measurement. The baseline triplicate readings for blood pressure will be averaged for eligibility determination.

7.1.3 Electrocardiogram

12–lead ECG should be recorded after participants have been resting at least 5 minutes in the supine position. Digital ECG tracings will be performed using equipment from and analyzed by a central ECG laboratory. The cardiologist reading the ECGs will be blinded regarding study drug assignment. All standard intervals will be measured.

When assessing eligibility at the Screening visit, the presence of BBB (either left or right) is allowable as long as the absolute QTcF value does not exceed 500 msec and the subject does not have any other cardiac exclusions as described in exclusion criterion 19. When an ECG displays a paced rhythm indicating a functioning pacemaker is present, there is no upper QTcF limit as long as there are no related cardiac exclusions (reference exclusion criterion 20). Note: If there is no known

history of BBB (either right or left), the discovery of such should prompt further investigation prior to proceeding with screening.

At the Baseline visit, the participant will have an ECG obtained (in triplicate) in order to verify continued eligibility for the study. If the QTcF is >470 msec is determined based on the average of the 3 QTcFs obtained from the local reading, a subject should not be dosed, pending central reading of the ECG.

When the site receives the Baseline Visit Central ECG Laboratory reading(s), if QTcF is confirmed as exclusionary (using the criteria immediately above), the subject should be excluded. If the central reading does not confirm the exclusion, the patient may be dosed as soon as convenient/possible. If a patient was dosed based on local reading that determined to be acceptable (using the criteria above) and the central reading is nevertheless determined to be exclusionary, the site should contact the Sponsor for guidance on how to proceed.

At any time during the study, a subject with any of the above ECG values should prompt a call to the Sponsor for guidance on how to proceed.

7.1.4 Physical Examination

Complete physical examination will include skin, eyes, ears, nose and throat, cardiac, respiratory, abdomen, and extremities. Complete physical examination will be conducted at the Screening visit. Brief physical examination will include skin, eyes, oral mucosa, cardiac, and respiratory, and a directed exam related to any reported AEs. A brief physical examination will be conducted at all the study visits. Body weight will be also examined at all study visits.

Clinically relevant findings noted at Screening will be considered medical history. Any treatment emergent new finding on brief physical examination will be documented as an adverse event.

7.1.5 Neurological Examination

Complete neurological examination will include cortical function, meningeal irritation assessment, cranial nerves, motor and sensory function, coordination, deep

tendon reflexes, stance and gait. Complete neurological examination will be conducted at Screening.

Brief neurological examination will include meningeal irritation assessment, cranial nerves, motor and sensory function, coordination, deep tendon reflexes, stance and gait. Brief neurological examination will be conducted at all the study visits.

Clinically relevant findings noted at Screening will be considered medical history. Any treatment emergent new finding on brief neurological examination will be documented as an adverse event.

7.1.6 Laboratory

7.1.6.1 Standard Safety Laboratory Tests

Unless noted otherwise, safety laboratory tests will be performed in the fasted state, according to the Schedule of Activities in Table 1 and Table 2. All routine laboratory tests will be analyzed by a central laboratory that will provide instructions and supplies.

Hematology	Chemistry	Urinalysis	Other[c]
Hemoglobin Hematocrit RBC count Platelet count WBC count MCV Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and Creatinine Plasma Glucose (fasting) Calcium Sodium Potassium Chloride Total CO2 (Bicarbonate) AST ALT GGT LDH Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein HbA1c Insulin eGFR calculation	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy[a]	FSH[b] Urine drug screen T3, T4, TSH Vitamin B12 Hepatitis B, C

a Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b Females.
c At screening.

- Hepatitis screens include hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, and hepatitis C antibody.

- Minimum requirement for urine drug testing includes: cocaine, THC, opiates, benzodiazepines and amphetamines.

7.1.6.2 Assessment of Blood Glucose Using Point of Care Device

An on-site point of care blood glucose measurement must be obtained prior to neuropsychological assessments. The point of care blood glucose measurement should be obtained after an appropriate time following the low carbohydrate / high protein meal or snack (e.g., 30-60 minutes). The blood glucose measurement obtained using the point of care device will only be documented in the source documents and used to determine if it is appropriate to proceed with neuropsychological assessments.

The blood glucose measurement from the central laboratory will be the measurement included in the study database.

7.1.6.3 Assessment of Potential Cases of Drug Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below, in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury. These events should be considered important medical events and reported as serious adverse events.

Participants who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

a. Participants with AST or ALT baseline values within the normal range who subsequently present with AST or ALT ≥3 times the upper limit of normal concurrent with a total bilirubin ≥2 times the upper limit of normal with no evidence of 1) hemolysis, 2) cholestasis (elevated alkaline phosphatase ≥2 times the upper limit of normal or not available) or 3) Gilbert's Syndrome (common benign condition associated with intermittent elevations of primarily indirect, unconjugated, bilirubin to about 2 X upper limit of normal.)

b. Participants with pre-existing AST or ALT baseline values above the normal range who subsequently present with AST or ALT ≥2 times the baseline values and ≥3 times the upper limit of normal concurrent with a total bilirubin ≥2 times the upper limit of normal with no evidence of 1) hemolysis, 2) cholestasis (elevated alkaline phosphatase ≥2 times the upper limit of normal or not available) or 3) Gilbert's Syndrome (common benign condition associated with intermittent elevations of primarily indirect, unconjugated, bilirubin to about 2 X upper limit of normal.)

Increases defined above should be confirmed with repeat testing within 48 to 72 hours. In addition to repeating AST and ALT, laboratory tests should include albumin, amylase, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. Symptoms should be assessed. The medical monitor should be contacted to discuss the patient's condition.

Close observation should be immediately initiated if symptoms persist and/or repeat testing confirm the abnormalities described above. Evaluation should include repeating laboratory tests (two or three time weekly; frequency may decrease to once a week or less if abnormalities stabilize or trial drug is discontinued and the subject is asymptomatic), and a detailed medical history and physical assessment. A detailed history, including relevant information, such as history of symptoms or concurrent illnesses, concomitant medication use (including review of acetaminophen use and herbal/dietary supplements), alcohol consumption, recreational drug use and special diets. Additionally, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Ruling out acute hepatitis A, B, C, D, and E infection, autoimmune or alcoholic hepatitis, NASH, hypoxic/ischemic hepatopathy, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, parvovirus and biliary tract disease (gall bladder/ductal imaging may be warranted).

All cases confirmed on repeat testing, with no other cause for LFT abnormalities identified at the time should be considered potential drug induced liver injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs.

7.2 NEUROPSYCHOLOGICAL ASSESSMENTS

The following cognitive/functional/global test batteries will be conducted at selected time points as described below and in the Schedule of Activities.

If a participant presents at any visit with any condition that, in the opinion of the investigator, may jeopardize the accurate evaluation of participant's neuropsychological function, participants should not receive neuropsychological tests, and reserve an additional visit to evaluate function within the allowance of the visit window.

Neuropsychological assessments must not be performed if the patient is fasting; neuropsychological assessments should be performed following the meal/snack and blood glucose measurement, during a study visit. The same rater should follow a particular participant for any given assessment for the duration of the study whenever possible. The scales are to be administered to the subject in the following order when they occur at the same visit: MMSE, ADAS-cog, CDR (patient portion), C-SSRS. All neuropsychological assessments must be performed by a trained rater.

- Non-CDR Rater – This person will meet the education, clinical and scale experience requirements set by the sponsor. This person can conduct all ratings and assessments, once qualified by the rater training staff, except for the CDR. If appropriately qualified, the PI or Study Coordinator may also fulfill this role.

- CDR Rater – This person will render the CDR rating based on clinical assessment of participant and caregiver / study partner, using scale worksheets provided by the Sponsor, but without access to the ADAS-cog or any other study assessments. Neither the PI nor the Study Coordinator responsible for study oversight may fulfill this role.

7.2.1 Cognitive Assessments

Mini Mental State Examination (MMSE): The MMSE is a brief 30-point test that is used to assess cognition (Folstein, 1975). It is commonly used to screen for dementia. In the time span of about 10 minutes, it samples various functions, including arithmetic, memory and orientation. The MMSE will be administered according to the Schedule of Activities in Table 1 and Table 2. Scores range from

0-30 with lower scores indicating greater cognitive impairment. Participants with scores of 21-26 at Screening and scores of 19-27 at Baseline will be eligible for participation in the study. The MMSE must always be administered in a fed state.

Alzheimer's Disease Assessment Scale - Cognitive Subscale 90 point (ADAS-cog14): The 14-Item Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog14) is a structured scale (approximately 45 minutes to complete) that evaluates memory, orientation, attention, reasoning, language, constructional praxis, delayed recall, digit cancellation, and maze-completion. The ADAS-cog14 scoring range is from 0 to 90, with higher scores indicating greater cognitive impairment (Mohs et al. 1997). The ADAS-cog will be administered according to the Schedule of Activities in Table 1 and Table 2. Participants with scores of ≥10 at Screening and Baseline will be eligible for participation in the study. The ADAS-cog must always be administered when the subject is in a fed state.

7.2.2 Functional/Global Assessments

Functional Activities Questionnaire (FAQ): The FAQ is an inventory of instrumental activities of daily living developed by (Pfeffer 1982). The FAQ is administered by asking the informant to rate patient's ability (0-3) on 10 different activities of daily living. The total FAQ score ranges from 0 to 30, with higher scores indicating greater functional loss. The FAQ will be administered according to the Schedule of Activities in Table 1 and Table 2.

Amsterdam-Instrumental Activities of Daily Living Questionnaire (A-IADL): The A-IADL is an adaptive questionnaire designed to assess impairments in instrumental activities of daily living in early dementia.(Sikkes 2013) The questionnaire is completed by a caregiver / informant. The original questionnaire consists of 70 items in seven categories and the administration time is approximately 20-25 minutes. The A-IADL total score is calculated using an item response theory method of scoring and lower scores indicate greater functional impairment. The A-IADL will be administered according to the Schedule of Activities in Table 1 and Table 2.

Clinical Dementia Rating Scale (CDR): The CDR scale is used as a global measure of dementia and is completed by a clinician in the setting of detailed knowledge of the individual patient collected from interviews with the caregiver (first) and patient

(second).(Berg, 1988) The CDR describes 5 degrees of impairment in performance on each of 6 categories including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The interview takes approximately 40 minutes to administer.

CDR global ratings are 0 for cognitively unimpaired individuals, 0.5 for questionable dementia and 1, 2 and 3 for mild, moderate and severe dementia as defined in the CDR scale. The scores for each category can also be summed and this is known as the sum of box score (CDR-SB). Sum of box scores range from 0 to 18 with higher scores indicating greater cognitive impairment.

The CDR will be administered according to the Schedule of Activities in Table 1 and Table 2 and the subject must in a fed state.

7.2.3 Other Assessments

Neuropsychiatric Inventory (NPI): The NPI is a well-validated, reliable, multi-item instrument to assess psychopathology in AD based on an interview with the caregiver.(Cummings 1994) The interview is also relatively brief (15 minutes). It evaluates both the frequency and severity of 12 behavioral areas including delusions, hallucinations, dysphoria (depression) anxiety, agitation/aggression, euphoria, disinhibition, irritability, lability, apathy, aberrant motor behavior, appetite and eating changes and night-time behaviors.

Frequency assessments range from 1 (occasionally, less than once per week) to 4 (very frequently, once or more per day or continuously) as well as severity (1= mild, 2 = moderate, 3 = severe). Distress is rated by the study partner or caregiver and ranges from 0 (no distress) to 5 (very severe or extreme). The overall score and the score for each subscale are the product of severity and frequency. Scores range from 0-144 with higher scores indicating a greater presence of neuropsychiatric symptoms. The NPI will be administered according to the Schedule of Activities in Table 2.

Dementia Quality of Life (DEMQOL) –Proxy: The DEMQOL-Proxy questionnaire is a validated and reliable questionnaire that is interview administered and completed by the caregiver about the patient's health related quality of life.(Smith 2005) It consists of 31 items representing 5 domains (daily activities and looking after

yourself, health and well-being, cognitive functioning, social relationships, and self-concept) and takes approximately 20 minutes to complete. Higher scores indicate better health related quality of life. This scale will be administered at according to the Schedule of Activities in Table 2.

7.3 SUICIDALITY ASSESSMENTS

The Columbia Suicide Severity rating Scale (C-SSRS) is a joint interview with the caregiver and patient that systemically assesses suicidal ideation and suicidal behavior.(Posner 2011) This scale will be administered at Screening Visit to evaluate life time suicide attempt, suicide behaviors, and other non-suicidal self-injuries. The CSSRS must be administered by a certified rater. Positive responses on the C-SSRS will be mapped to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for classification and reporting using a standard algorithm.

At the Screening and Baseline Visit, the C-SSRS will be used to detect possible suicidality prior to dosing. If the patient's responses indicate: (1) the subject may have had suicide ideation associated with actual intent and/or plan in the past year, (2) any history of suicidal behavior in the past 10 years, (3) any lifetime history of recurrent suicidal behavior the subject should be excluded. In the event that the subject answers "Yes" to the suicidal ideation items 4 or 5 of the C-SSRS or a history of suicidal behavior within the previous 10 years as indicated by a "yes" answer to any of the suicidal behavior items of the C-SSRS at the screening or baseline visit, that subject will not be eligible for inclusion in the study.

Following dosing, the C-SSRS will be used to assess suicide ideation or behavior at each study visit. Following dosing (after the Baseline / Randomization visit), if there are "yes" answers on items 4, 5 or on any behavioral question of the C-SSRS, a professional suicide risk assessment must be done as soon as possible to determine whether it is safe for the subject to continue participation in the trial. A risk assessment will be done by an independent, qualified mental health professional with expertise in the evaluation of suicidality in the elderly (e.g., psychiatrist, geriatrician or neurologist specializing in treatment of patients with AD) to determine whether it is safe for the subject to participate in the study. Neither the PI nor any member of the PI staff may conduct this interview. A change from baseline to a yes on any of these items will also constitute an AE and must be documented as such.

7.4 PLASMA FOR ANALYSIS OF AZELIRAGON AND METABOLITE CONCENTRATIONS

Blood samples for pharmacokinetic (PK) analysis of azeliragon and metabolite concentrations will be collected according to the Schedule of Activities in Table 1 and Table 2.

All PK Blood samples to provide plasma for pharmacokinetic analysis will be collected, processed, stored, and shipped according the lab manual instructions.

Samples will be analyzed using a validated analytical method.

The shipment address and assay lab's contact information will be provided to the investigator site prior to initiation of the trial.

7.5 PLASMA FOR ANALYSIS OF TOTAL Aβ, Aβ (1-40), Aβ(1-42)

Blood samples for plasma biomarkers analysis will be collected according to the Schedule of Activities in Table 1 and Table 2.

Blood samples for plasma biomarkers will be collected, processed, stored, and shipped according the lab manual instructions.

7.6 MRI

MRI scans will be performed at Screening in Part 1 and at Screening and Month 18 / Early Termination in Part 2. MRI scans will be read by a central reader prior to inclusion in the study to detect any exclusionary conditions such as stroke, hematoma, or intracranial tumor. The screening MRI should be performed at least 14 days prior to dosing to allow for the central read and interpretation of results prior to dosing. A local read is not required. Outside or prior MRI scans will not suffice for inclusion.

Specific MRI scan sequences required for safety and/or volumetric assessments will be outlined in the MRI procedures manual. Participants will be monitored, and images will be reacquired if there is subject movement during the scan. Volume,

surface area, and thickness values for all Freesurfer-generated regions will be assessed.

Brain magnetic resonance imaging (MRI) may include gadolinium contrast if the investigator determines that this is necessary for patient care either based on clinical signs or findings on the non-contrast MRI. Gadolinium may also be used when considered the standard operating procedure for the study site. Gadolinium should not be administered if the glomerular filtration rate <30 mL/min or equivalent creatinine clearance. However, this decision may be made by the PI on the basis of a change in the clinical status or may be done in response to a possible abnormality seen on the non-contrast brain MRI.

An MRI Imaging CRO will be responsible for standardizing the acquisition, training the MRI sites on the imaging protocol, ensuring equipment and image QA/QC and for overseeing a centralized read of the data. To ensure proper equipment and image QA/QC, the MRI Imaging CRO will have the MRI sites scan a phantom. Detailed procedures for obtaining and processing the MRI, conducting image QA/QC and endpoint analysis will be developed in study specific documents and provided as appropriate to the investigators, MR technicians, CRO personnel and endpoint readers.

Analysis of whole brain, ventricular, and hippocampal volumes will be conducted by a centralized reader(s) who will be blinded to subject treatment.

7.7 CT SCANS

A head CT scan may be accepted for evaluation of the eligibility criteria on a case-by-case basis, as approved by the Sponsor (e.g., when MRI is contraindicated for the subject). The head CT must be suitable for central review and submitted for central review based on instructions in the MRI procedures manual.

Subjects whose screening assessment was based on a CT scan will not undergo a follow-up CT scan (Part 2 only) and will not contribute to the MRI volumetric analyses (Part 2 only).

An Imaging CRO will be responsible for providing guidance on the imaging procedure. Sites will be advised to acquire the CT per their standard clinical practice. Scans will be reviewed by the Imaging CRO central reader.

7.8 APOE GENOTYPING

A blood sample will be taken at Baseline for ApoE genotyping. Results of ApoE genotyping will be retained in the trial database, with participants identified only by a study participant identification number. Individual results of ApoE genotyping will not be disseminated outside the Sponsor, including the study site, except as required by law.

7.9 BLOOD SAMPLING FOR STORAGE AND RETENTION

A blood sample will be collected according to the Schedule of Activities in Table 1 and Table 2. Blood samples for whole blood and plasma storage/retention will be collected, processed, stored, and shipped according the lab manual instructions.

Samples will be stored for up to 2 years following study closure for potential future analysis for plasma biomarkers associated with AGEs, RAGE expression, or RAGE antagonist response that may be identified during the course of the trial.

Instructions on collection, processing, storage and shipment of the sample will be provided in a separate laboratory manual.

7.10 BLOOD VOLUME

Total blood sampling volume for the individual participants is approximated below for Part 1 (Table 4) and Part 2 (Table 5) participants.

Table 4. Part 1 Blood Sampling Volumes

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening / Baseline	Treatment	Non-treatment Follow-up	
Routine Laboratory	12	2	2	1	60
Unique Screening Labs	12	1	0	0	12
PK	5	1	2	1	20
Biomarkers (Aβ)	10	1	2	1	40
ApoE Genotyping	3	1	0	0	3
Plasma Storage and Retention	10	1	2	1	40
TOTAL (mL)					175

Table 5. Part 2 Blood Sampling Volumes

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening / Baseline	Treatment	Non-treatment Follow-up	
Routine Laboratory	12	2	6	1	108
Unique Screening Labs	12	1	0	0	12
PK	5	1	6	1	40
Biomarkers (Aβ)	10	1	6	1	80
ApoE Genotyping	3	1	0	0	3
Plasma Storage and Retention	10	1	6	1	80
TOTAL (mL)					323

8.0 ADVERSE EVENT REPORTING

8.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a clinical study participant administered a pharmaceutical product. Study drug treatment does not necessarily have a causal relationship with the AE. An AE, therefore, can be any unfavorable change in structure, function or chemistry (including abnormal clinical lab results, or ECG findings), symptoms, signs, or diseases temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product, as defined by ICH.

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.2 REPORTING PERIOD

Adverse event reporting will commence as soon as the study participant has been dosed, unless the event is deemed to be related to study procedures. The study-related procedure might include discontinuation from or decrease in current therapy, a study-specific assessment or scale, or a study-specific procedure. Events associated with such study- specific procedures prior to initial administration of study drug will be tracked as AEs from the time when the study participant signed the ICF.

SAE reporting will commence from the time the participant provides informed consent through last subject visit. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to study treatment is suspected.

All events, including pre-existing conditions that are not associated with study-specific procedures, which worsen after the study participant has signed the ICF, but occur prior to initial administration of study drug, are not considered AEs and will be captured under medical history. However, worsening of such conditions after initial administration of study drug will be designated as AEs.

8.3 ASSESSMENT OF SEVERITY

The following definitions of severity should be used in the evaluation of AEs:

- Mild: an AE that is easily tolerated and does not interfere with a subject's usual function or daily activities.
- Moderate: an AE that is sufficiently discomforting so as to interfere to some extent with a subject's usual function or daily activities.
- Severe: an AE that interferes significantly or prevents a subject's usual function or normal everyday activity.

The adjective selected should describe the maximum intensity of the adverse event.

8.4 ASSESSMENT OF RELATIONSHIP TO STUDY DRUG

The Investigator's assessment of causality must be provided for all adverse events (serious and non-serious) and recorded in the eCRF. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the Investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

The following definitions of relationship to study drug should be used to characterize the suspected causality of each AE, based on the Principal Investigator 's or licensed physician consideration of all available information:

- Related: There is evidence to suggest a causal relationship between the study drug and the AE.
- Not Related: The AE is not reasonably related to the study drug if there is not a reasonable possibility that the study drug may have caused the event, i.e., there is no evidence or arguments to suggest a causal relationship.

8.5 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any AE that is fatal or life-threatening (see below), results in persistent or significant disability (see below) or incapacity, requires inpatient hospitalization or prolongation of an existing hospitalization, or is a congenital anomaly/birth defect.

Other important medical events that may not result in death, be life-threatening or require hospitalization should also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the study participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or convulsions that do not result in inpatient hospitalization.

8.5.1 Life Threatening Adverse Event

A life-threatening AE is any AE that, in the view of the Principal Investigator, places the subject at immediate risk of death from the reaction as it occurred. A life-threatening AE would not be an AE that, had it occurred in a more serious form, might have caused death.

8.5.2 Disability

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

8.5.3 Unexpected Adverse Event

An unexpected adverse drug experience is defined as "any adverse drug experience, the specificity or severity of which is not consistent with the current IB. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB only listed cerebral vascular accidents. Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the IB), rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Unexpected adverse events should be reported to the IRB/ Research Ethics Board (REB) as per IRB/REB reporting requirements.

8.6 DOCUMENTATION OF ADVERSE EVENTS

The condition of each study subject will be monitored throughout the study. Signs and symptoms of possible AEs may be observed by the staff, elicited by asking an open or indirect question (e.g., "How have you been feeling?") or volunteered by the subject. All AEs, whether observed by the Investigator or clinical site staff, elicited from the subject, or volunteered by the subject, will be recorded on the adverse event page(s) of the CRF. Data will include start and end dates, concomitant medications given for AE, Investigator-specified severity, relationship to study drug, and action taken. All AEs should be reported to the study Sponsor.

8.7 REPORTING REQUIREMENTS

Follow-up of any ongoing AE (including any clinically significant laboratory abnormality) should be conducted as follows:

- If the Investigator determines the AE is *not related* to the study product or study procedures, the AE will be followed until resolution, declared stable, or until the end of study participation.

- All AEs with a relationship of *related* will be followed until resolution, declared stable, or until the subject is lost to follow-up.

At the discretion of the Investigator or designated licensed physician and Medical Monitor, the length of AE follow-up may be attenuated, with written rationale by the Investigator or designated licensed physician.

8.7.1 Serious Adverse Events Reporting Requirements

Knowledge of a SAE occurring or worsening in a subject at any time during the trial must be reported within 24 hours to the Sponsor / Sponsor Representative. The site is responsible for reporting the event to the relevant IRB/REB in accordance with the IRB or REB's specific requirements for reporting SAEs. The Principal Investigator or designee should not wait to receive additional or follow-up information before an initial notification is made to the Sponsor.

Instructions related to SAE reporting, along with reporting forms and Sponsor contact information will be provided by the Sponsor to the Study Site and should be maintained in the Study Site File (SSF).

Reports relative to the subject's subsequent course must be submitted to the Safety Monitor until the event has subsided or, in the case of permanent impairment, until the condition stabilizes. These reports need not be submitted within 24 hours of first knowledge of each item of new information, unless the new information results in a change in diagnosis or represents a significant worsening of the subject's condition.

At any time following the study, the PI or designee should immediately notify the Sponsor and the IRB/REB if he/she learns of the occurrence of any death or malignancy involving the participant of a clinical trial or of any congenital anomaly in an offspring of a participant.

9.0 DATA ANALYSIS/STATISTICAL METHODS

The statistical considerations summarized in this section describe the protocol-defined plan for data analysis of this study. A final and complete Statistical Analysis Plan (SAP) will be finalized prior to unblinding the data from the learning stage of the study (Part 1), possibly updated prior to unblinding the confirmatory stage of the study (Part 2). The SAP will supersede the protocol. Any deviations from the planned analyses will be described and justified in the final integrated study report.

This trial describes two studies (learning stage and confirming stage) with a common infrastructure in a single protocol. Statistical analysis of the clinical efficacy variables will be done for each of the study studies separately. Analysis of MRI volumetric data only applies to part 2 of the study. Statistical evaluation of adverse events will be done by each part separately and also integrated for the study as a whole. Statistical analysis of safety measures that are collected by visit will be done for the study as a whole (combined).

Continuous variables will be presented showing number of observations available, mean, median, minimum, maximum, 1st and 3rd quartiles, and standard deviations (or standard errors, depending on the variable) by visit. Categorical variables will be presented showing frequencies and percentages by visit.

All tests will be 2-sided and use an overall study-wise $\alpha = 0.05$ unless otherwise stated. SAS Version 9.4 or later will be used. Medical dictionary for Regulatory Activities (MedDRA) Version 21.0 or later will be used for coding adverse events. Medications will be coded using WHO Drug Dictionary (WHODD) Version March 2018 or later.

This study features a conditional sequential approach to hypothesis testing to control alpha, similar to methods using Bauer closed procedures.

9.1 POTENTIAL ADAPTIVE FEATURES

This study is planned to conform to regulatory guidance depicted in the FDA guidance *Adaptive Designs for Clinical Trials of Drugs and Biologics* (draft guidance, September 2018).

Part 1 of the study will inform the selection of a functional endpoint to serve as co-primary in Part 2, as well as the sample size required to adequately power the study to detect treatment effect on cognitive and functional measures in the study population.

Consistent with the FDA draft guidance on adaptive designs, it is acknowledged that interim analysis is common in trials, and it includes blinded analysis or unblinded analysis. In this study, however, Part 1 is intended to be completed, the database locked, and the analysis done as a final analysis, thereby avoiding the need for the interim analysis.

The planned features of the confirmatory phase (Part 2) that will be subject to modification informed by the learning phase (Part 1) of the study are:

- Primary endpoint(s) for Part 2
- Sample size for Part 2
- Study duration for Part 2
- Eligibility criteria for Part 2
- Dose of study drug for Part 2

9.2 SAMPLE SIZE DETERMINATION

Sample size considerations for Part 1:

Assuming a standard deviation of the change from Baseline to Month 6 in ADAS-cog14 of 4, using alpha = 0.05, a total sample size of approximately 82 subjects in balanced allocation (41 subjects per group) provides at least 90% power to detect a difference between treatment groups of 2.9 using a 2-sided, 2-sample t-test. Assuming a dropout rate of 18% or less, randomization of 100 subjects provides adequate statistical power for Part 1 to demonstrate superiority of azeliragon over placebo based on the ADAS-cog14.

Sample size considerations for Part 2:

Assuming a standard deviation of the change from Baseline to Month 18 in ADAS-cog14 of 7.5, using alpha = 0.049 (to include an adjustment for potential alpha inflation due to the independent data monitoring committee reviews), a total sample size of 120 subjects in balanced allocation (60 subjects per group) provides at least 90% power to detect a difference between treatment groups of 4.5 using a 2-sided, 2-sample t-test. Assuming a dropout rate of 25% or less, randomization of 160 subjects provides adequate statistical power for Part 2 to demonstrate superiority of azeliragon over placebo based on the ADAS-cog14.

9.3 RANDOMIZATION AND BLINDING

9.3.1 RANDOMIZATION

This protocol includes two independent randomizations for the two stages of the adaptive study.

Subjects will be screened by Investigators or qualified designees to assess eligibility for randomization into the study. An interactive voice response system (IVRS)/ interactive web response system (IWRS) will be used for assignment of treatment.

For each stage of the study, subjects will be enrolled and randomized according to a fixed randomization scheme blocked by study investigative site. There is no other stratification in the randomization scheme for either stage of the study.

Randomization will have balanced allocation (1:1) between azeliragon and placebo. Dropouts will not be replaced.

A randomization plan will be developed to guide the programming and security of the randomization scheme for this study.

9.3.2 BREAKING THE BLIND

The study will be double-blind. At the initiation of the study, the study site will be instructed on the electronic process for breaking the blind. Blinding should only be broken in emergency situations when knowledge of the treatment assignments is

necessary for subject safety. Upon breaking the blind, the reason must be documented in the electronic data capture system. The sponsor or representative should be consulted prior to breaking the blind except in emergency circumstances.

9.4 STATISTICAL HYPOTHESES

The learning stage has a single primary endpoint while the confirming stage of the study has two co-primary endpoints. The conditional sequence of hypothesis tests applies to both, acknowledging that the imaging endpoints will not exist for the learning stage of the study.

For each stage of this adaptive study, a 2-stage conditional sequence of statistical hypothesis tests will be used. The testing sequence will be as follows:

The first set of hypotheses to be tested is as follows:

- H_{01}: The mean change in ADAS-cog14 in the active group active group is equal to that of the placebo group.
- H_{11}: The mean change in ADAS-cog14 in the active group is not equal (is superior) to that of the placebo group.

Conditional on statistical significance, testing will proceed:

- H_{02}: The mean change in CDR-sb in the active group is equal to that of the placebo group.
- H_{12}: The mean change in CDR-sb in the active group is not equal (is superior) to that of the placebo group.

Conditional on statistical significance, testing will proceed:

- H_{03}: The mean change in FAQ in the active group is equal to that of the placebo group.
- H_{13}: The mean change in FAQ in the active group is not equal (is superior) to that of the placebo group.

Conditional on statistical significance within the confirmatory stage, testing will proceed:

- H_{02}: The mean change in MRI variable of analysis in the active group is equal to that of the placebo group.
- H_{12}: The mean change in MRI variable of analysis in the active group is not equal (is superior) to that of the placebo group.

9.5 POPULATIONS OF ANALYSIS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following population of analysis will be used for all statistical analysis:

- The full analysis set (FAS) includes all randomized subjects who receive any study medication and have at least one post-Baseline assessment.
- The per protocol set (PPS) includes all subjects in the FAS, except for those who are excluded because of major protocol violations, where a major protocol violation is one that may affect the interpretation of study results (e.g., taking less than 50% of prescribed study medication during participation).

Final determinations of the PPS will be made at the masked data review meeting held in accordance with ICH E9 prior to the lock data. The complete specification (made blinded to treatment arm) will be documented in the minutes to the blind data review meeting held prior to lock the data.

- The safety set (SAF) includes all subjects who receive any study medication.

For the purpose of understanding the influence of dropouts on study conclusions, the FAS will be partitioned into subjects who complete (completers) and subjects who do not complete (dropouts).

The FAS will be used for all hypothesis tests of efficacy. Analysis of superiority using the PPS will also be done for supportive analyses. If the PPS does not differ from the FAS by at least 15%, the PPS is considered optional.

The SAF will be used for safety analyses.

9.6 DISPOSITION, DEMOGRAPHIC, AND BASELINE DATA

A tabulation of subject disposition will be presented, including the number screened, the number randomized in each population group, the number dosed in each population group, the number who withdrew prior to completing the study, and reasons for withdrawal.

Demographic and baseline characteristics will be summarized for all randomized patients and for the FAS. Variables of interest include the following:

- Age
- Sex,
- Race,
- Ethnicity
- Medical history
- Prior AD medication
- Height/weight/BMI
- Education level
- ApoE4-carrier status
- Years since diagnosis of AD
- Years since diagnosis of diabetes or HbA1c evaluation of 6.5% or more

Additionally, baseline characteristics will be compared for efficacy measures of MMSE, ADAS-cog14, CDR-sb, FAQ, Amsterdam IADL, ApoE4-carrier status, HbA1c. No formal statistical comparisons will be performed.

9.7 EFFICACY ANALYSIS

Efficacy evaluation will include the primary (ADAS-cog14 for Part 1) and co-primary endpoints (ADAS-cog14 and CDR-sb) for Part 2, key secondary measures, and other efficacy markers.

Statistical analysis will be done on each stage of the study, independently, for the primary / co- primary variables: change from baseline in ADAS-cog14 and change from baseline in CDR-sb. For all other secondary variables, and subgroup analyses, the study as a whole will be used for inferential purposes.

9.7.1 Efficacy Variables of Analysis

9.7.1.1 Primary Efficacy Variables of Analysis

The primary analysis will include assessment of the following variables of analysis.

Learning stage (Part 1)

- Mean change from Baseline to Month 6 in ADAS-cog14

Confirm stage (Part 2)

- Mean change from Baseline to Month 18 in ADAS-cog14
- Mean change from Baseline to Month 18 in CDR-sb

Supportive variables will include mean change from Baseline to Visit in ADAS-cog14 and mean change from Baseline to Visit in CDR-sb.

9.7.1.2 Secondary Variables of Analysis

Part 1 secondary variables of analysis will include.

- Mean change from baseline in CDR-sb at Month 6.
- Mean change from baseline in the FAQ at Month 6.
- Mean change from baseline in the Amsterdam-IADL at Month 6.
- Mean change from baseline in eGFR at Month 6.

Part 2 will include the following secondary variables of analysis:

- Time to decline (to support responder analysis) where the specification of decline will be included in the SAP.

- Mean change from baseline in FAQ score at Month 18
- Mean change from baseline in Amsterdam-IADL score at Month 18
- Mean change from baseline in MMSE score at Month 18
- Mean change from baseline in eGFR at Month 18.
- Mean change from baseline in whole brain volume at Month 18.

9.7.1.3 Other Efficacy Variables of Analysis

Additional efficacy variables of analysis are as follows:

- Mean change from Baseline in hippocampal volume at Month 18.
- Mean change from Baseline in ventricular volume at Month 18.
- Mean change from Baseline in NPI
- Mean change from Baseline in DEMQOL.

9.7.2 Statistical Methodology for Primary Analysis

The primary analysis will use the ITT methodology and a main-effects mixed-models for repeated measures (MMRM) methodology. The MMRM will utilize an unstructured covariance where the number of parameters is "t(t+1)/2" where "t" is the dimension of the covariance matrix, using PROC MIXED in SAS. In the unlikely event of lack of convergence, Toeplitz structure will be employed where the number of parameters is "t" where "t" is the dimension of the covariance matrix. Time is considered as a class variable. Analysis will include treatment, time and treatment-by-time interaction as fixed effects, Baseline as covariate, and subject as a random effect. Supportive modeling will also include MMRM main-effects model with treatment, time, and subject.

Model assumptions will be evaluated. If the parametric assumptions are evaluated as inappropriate or violated, rank analogues will be advanced.

The primary analysis will be done for each stage separately. Part 1 will use alpha = 0.0499, which includes an adjustment of 0.0001 for interim analyses performed by the Independent Data Monitoring Committee (IDMC). The alpha adjustment for the IDMC for Part 1 is considered to be negligible, hence, the stated alpha for Part 1 is 0.05 for the 100-patient, 6-month trial. Part 2 will use alpha = 0.049, which includes an adjustment of 0.001 for interim analyses performed by the Independent Data Monitoring Committee (IDMC), thereby preserving the overall study-wise alpha = 0.05. The alpha adjustment of 0.001 is considered to be appropriate for the 200-patient, 18-month study.

Multiple imputations (MI) will be used as a supportive analysis with 100 invocations (acknowledging that more invocations are needed with more missing data). Monte Carlo methods are planned.

An essential component of the thorough analysis includes an assessment of the impact of missing data on study conclusions. As a part of assessing this impact, supportive analysis will include:

- an endpoint analysis (reduction to last-observation-carried-forward, justified in this study based on the monotonic progression of the natural course of AD and assuming no more dropouts in the group treated with azeliragon than in the group treated with placebo)
- a completers analysis (observed cases at endpoint)
- observed cases by assessment time.

Interaction terms will be examined in supportive analyses. In the event of a significant interaction term, the impact on analysis conclusion will be examined. The primary model will not include interaction terms. A key supportive analysis will use the ITT methodology and a main-effects model for ANCOVA adjusting for baseline ADAS-cog14 (CDR-sb) using last-observation-carried-forward (LOCF) methods for missing data, justified based on known profiles of ADAS-cog14 (CDR-sb) in AD patients, which is conservative under the assumption that there are not more dropouts in the active-treated group than the placebo group. Rank ANCOVA will be done as a supportive analysis.

To ensure robustness of analysis conclusions against missingness, multiple imputation methods will also be done to cope with missing data as a key supportive analysis using the final on-treatment assessment of treatment failures as non-missing data at endpoint.

In accordance with the recommendations of the report from the National Academy of Science (NAS) panel "*The Prevention and Treatment of Missing Data in Clinical Trials*," (National Research Council, 2010), missingness is classified as "missing at random" (MAR) or "missing not at random" (MNAR). When subjects are withdrawn due to treatment failure, this event is considered in this sensitivity analysis to be MNAR, and the endpoint value is taken as the hard endpoint (not imputed) in analysis, operationally, the endpoint analysis is the same as LOCF. Data that are missing for other reasons are considered to be MAR, and standard multiple imputation methods are planned.

Descriptive summaries will be produced of the observed values and change from Baseline in co-primary variables by treatment group at each individual time point and at endpoint (final on-treatment assessment for each subject).

For statistical analyses, 95% confidence intervals will be produced for the least-squares means (LSM) in each treatment group, as well as the LSM differences as compared to placebo. For MMRM and ANCOVA, two-sided p-values will be displayed for the comparison against placebo.

Because there are limited numbers of subjects per center, there will inadequate power to explore impact of the center effect on study conclusion. Descriptive statistics by center will be presented.

The primary analysis controls alpha through the conditional sequence of hypothesis testing. No further adjustment for multiplicity is necessary.

If the PPS differs from the FAS by more than 15%, the analyses will be replicated on the PPS. If the PPS and the FAS do not differ by more than 15%, analysis may not be done on the PPS. Final judgments will be made at the blind data review meeting in accordance with ICH E9.

9.7.3 Statistical Methodology for Secondary and Other Efficacy Analysis

Secondary and exploratory endpoints that are measurement variables will use similar statistical methodology to the methodology used for primary analysis. Efficacy variables that are proportions will be analyzed using Mantel-Haenszel test. For the analysis of the categories for responders, a Cochran-Mantel-Haenszel test will be used.

Methodologies for variables that are proportions will include construction of confidence intervals for each treatment group and for the difference between groups. For analysis, Fisher's exact test will be used for single-population analysis, and a Mantel-Haenszel test will be used for analyses combining data across strata.

Methodologies for time-to-event variables will include construction of 95% confidence intervals for each group separately and for the difference between groups. For analysis, a Wilcoxon test will be used for single-population analysis, and a van Elteren test will be used for analyses combining data across strata.

Subgroup analyses will be done as identified in the SAP.

Responders based on the ADAS-cog14 total score will be described using Kaplan-Meier curves using the specification of responder (lack of decline) provided in the SAP. Also, a graphical representation will be defined where the y-axis will show the cumulative percentage of patients who achieved the specific measure of improvement in the ADAS-cog14 total score shown on the x-axis with a separate cumulative percentage curve for each treatment group.

If the distribution of any of the above parameters, key secondary, or other secondary endpoints does not appear to be normally distributed, the rank analogues will be advanced.

9.7.4 Subgroup Analyses

The SAP will include details for subgroup analysis.

9.7.5 Adjustment for Multiple Comparisons

Multiplicity of the primary efficacy analyses is controlled by using a conditional sequence of hypotheses. The study will be considered to demonstrate statistical significance if the primary analysis has a resulting p-value less than 0.05. No other adjustment for multiplicity is required.

9.8 SAFETY ANALYSIS

The SAF is used for safety analysis. Adverse events, ECGs, vital signs and safety laboratory data will be reviewed and summarized on an ongoing basis during the trial to evaluate the safety of participants.

9.8.1 Safety Variables of Analysis

9.8.1.1 Adverse Events

Definitions:

- A *treatment-emergent adverse event* (TEAE) is an event that is observed or reported after administration of study medication that was not present prior to study medication administration or an event that represents the exacerbation of a pre-existing event.
- An *adverse withdrawal* is a subject who withdrew from the study due to an adverse event.
- A *serious adverse event* (SAE) is an AE that is classified as serious according to the criteria specified in the study protocol.

Adverse events variables of analysis include:

- Proportions of subjects with TEAEs by Preferred Term and decreasing frequency of TEAE
- Proportions of subjects with TEAEs by System Organ Class and Preferred Term
- Proportions of subjects with adverse withdrawals

9.8.1.2 Vital Signs

Vitals signs measures of blood pressure and pulse will include the following variables of analysis:

- Mean values and mean changes of values from Baseline to Visit
- Proportions of subjects with abnormal values or changes in vital signs measures of potential clinical concern.
- Proportions of subjects with AEs related to vital signs

9.8.1.3 Clinical Laboratory

Clinical Laboratory hematology and clinical chemistry variables of analysis include:

- Proportions of subjects with TEAVs (shifts from normal status to abnormal status)
- Proportions of subjects meeting DILI criteria per FDA guidance, *Guidance for Industry "Drug-induced liver injury: premarketing clinical evaluation"* (CDER, CBER, July 2009)
- Means and mean changes from Baseline to Visit
- Proportions of subjects with new (post Baseline) values (Clinical laboratory-related AEs) or changes in laboratory values of potential clinical concern

9.8.1.4 Electrocardiography

Electrocardiography variables of analyses will include:

- Proportion of subjects with Corrections to QT intervals will be made by Fridericia's method. Categorical analysis will be done consistent with ICH E14, "Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs" (October 2005).

9.8.2 Statistical Methodology for Safety Analysis

Adverse events will be coded using MedDRA Version 21.0 or above. Adverse event coding will be done to the lowest level term (LLT). All treated patients will be included in the assessment of safety. Adverse events will be summarized by MedDRA System Organ Class and Preferred Terms. Separate tabulations will be produced for related AEs (those considered by the Investigator as drug related), SAEs, discontinuations due to AEs, and severe events.

Vital signs, ECG results, and laboratory data will be tabulated for changes over time on study. In addition, TEAV and significant findings will be summarized.

For each post-Baseline assessment, descriptive statistics are provided for the assessment value and the change from Baseline to the assessment.

9.9 PHARMACODYNAMIC DATA

All participants with at least one dose of study medication will be included in the pharmacodynamic analyses, as appropriate. For individual endpoints, participants must have at least 1 post-dose pharmacodynamic measurement for the given endpoint. For change from Baseline, participants must also have a Baseline value.

Plasma Aβ (total, 1-40 and 1-42) concentration and cerebral brain volume (hippocampus and whole brain, ventricular) versus time will be tabulated and mean concentration or brain volume versus time will be plotted for each treatment group. Descriptive statistics for raw and change from baseline values will be generated, as appropriate. Maximum and average change from Baseline values will be calculated by treatment group.

The statistical methods will be described in the SAP.

9.10 PHARMACOKINETIC DATA

Data resulting from blood sampling for trough concentrations of azeliragon will be collected and summarized descriptively. Concentration-driven analysis of the relationship between azeliragon (and potentially metabolite concentrations) and

efficacy/safety may be performed. The statistical methods will be described in the SAP.

9.11 QUESTIONNAIRES

Questionnaires include cognitive assessment, functional assessments, behavioral assessments, and assessments of quality of life. Questionnaires in this study will be scored according to the published guidelines provided in validation and documentation for the instruments by the developers. The statistical methods will be described in the SAP.

9.12 HANDLING MISSING DATA

Data are considered to be "on-treatment" if the assessment of collection follows the first administration of study medication and if the assessment occurs within 45 days following the final administration of study medication, justified based on the long half-life of this drug.

In general, for primary efficacy analysis and for safety analysis, missing data will not be imputed. Dates with missing fields will not have days imputed.

In accordance with the recommendations of the report from the National Academy of Science (NAS) panel "*The Prevention and Treatment of Missing Data in Clinical Trials*," (National Research Council, 2010), sensitivity analyses will be done to ensure that study conclusions are robust against missing data. Last observation carried forward (LOCF) and baseline observation carried forward (BOCF) methods will be used as appropriate in sensitivity analysis. Missing data types will be examined, and statistical methodologies for appropriate sensitivity analyses will be finalized during blind data review as patterns emerge as the study progresses. Primary methodologies following the ITT principle are not subject to change.

Details of methodologies identifying data as missing at random (MAR) or not missing at random (NMAR) will be addressed in the SAP. Statistical methods for addressing MAR and NMAR will be described in the SAP.

9.13 DATA MONITORING COMMITTEE

An external Independent Data Monitoring Committee (IDMC) will be responsible for the review of all available safety data at their regularly scheduled meetings during the trial.

The IDMC will consist of at least 3 members, including a neurologist who has experience in the treatment of individuals with AD and a senior statistician. Ad hoc members (e.g., experts on RAGE mechanisms or a cardiovascular physician) will be available for consultation by the IDMC upon request.

The IDMC will initially be provided with data displays in accordance with the IDMC charter.

Blinded summary IDMC reports will also be distributed to all participating sites for local IRB/REB submission, where applicable. The IDMC will meet in person or by conference call on a quarterly basis. The IDMC charter will specify these and other operational aspects of the IDMC structure, processes and study stopping rules.

9.14 INTERIM ANALYSIS

Except for the ongoing, blinded medical monitoring of accruing data and except for the ongoing review by the IDMC, no interim analysis is planned for Part 1 or Part 2.

Although this study has an adaptive design, and sample size re-estimation for Part 2 of the study is a potential feature for revaluation, the analysis of Part 1 to be used for the re-estimation is to be done as a final analysis following the database lock, hence, the analysis will not be an interim analysis. It is acknowledged that a blinded analysis is considered an interim analysis in accordance with the draft guidance from the FDA on adaptive designs, and no interim analysis is intended for this study.

As a conservative measure, an alpha adjustment is applied to accommodate analyses by the IDMC because the safety evaluation will include review of ADAS-cog14 data from the safety perspective. Alpha = 0.0001 is divided among no more than 4 interim analyses in the 100-subject, 6-month trial (for an alpha adjustment of 0.0001, which is considered to be negligible, so alpha=0.05 is available for the final analysis); for Part 2, alpha = 0.0001 is apportioned to each of no more than 10 analyses by the

IDMC that includes review of ADAS-cog14 data, blinded unless there is a data-driven need expressed by the IDMC to be unblinded.

With the possible exception of the IDMC, no unblinding is planned in this study for any reason other than emergency unblinding for medical imperatives.

It is emphasized that there is no interim analysis in this study for efficacy. The interim analyses described in this section refer to the analyses done by the IDMC for safety monitoring only.

9.15 DATA MANAGEMENT CONSIDERATIONS

This study will utilize electronic data capture (EDC) for data capture. The database lock will occur when each Part of the study is declared closed, when all subjects have completed the study part (last visit of the last subject on-study).

10.0 QUALITY CONTROL / MONITORING OF THE STUDY

During study conduct, the Sponsor or its designee will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. Additionally, the study site may be subject to quality assurance audits performed by the Sponsor, and/or to inspection by the IRB/REB or regulatory authorities.

11.0 DATA HANDLING AND RECORD KEEPING

11.1 CASE REPORT FORMS/ELECTRONIC DATA RECORD

This study will utilize electronic data capture (EDC) for the data record serving as the "Case Report Form (CRF)". All required study information must be recorded on the appropriate CRF screens/forms using the eCRF Completion Guidelines for the study. Quality control measures will progress final data management activities from last-patient-last-visit to database lock, then unblinding, final analysis, and final reported for each part of the study. The database lock will occur when the study is declared closed, when all participants have completed the study (last visit of the last subject on-study) and the data are fully monitored with all queries resolved.

The PI is responsible for ensuring that the data collected is collected/reported in a timely manner and is accurate, complete and legible. Data will be verified within the eCRF by the Study Site and the Study Monitor before being exported. Any changes made during verification will be documented with a full audit trail.

Any missing or inconsistent data entries will be referred back to the PI or designee, using a data query form, and documented for each individual study participant before eCRFs are frozen and signed by the PI. From that point forward, the database will be protected from changes (database lock).

11.2 RECORD RETENTION

For sites in the United States, the PI/Study Site must retain all study records, including regulatory documents and individual study participant records, for a period of 2 years following the date a marketing application is approved for the drug, for the indication for which it is being investigated; or, if no application is to be filed, or if the application is not approved, until 2 years after the investigation is discontinued, and the FDA is notified or longer if requested by Sponsor (per 21 CFR 312.62).

For sites in Canada, the PI/Study Site must retain all study records, including regulatory documents and individual study participant records, for a period of 25 years after the date of completion of trial (per FDR C.05.012).

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation, closure of facility), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to vTv Therapeutics, such as another investigator, another institution, or to vTv Therapeutics. vTv Therapeutics needs to be notified and approval obtained before records may be transferred off site.

12.0 ETHICS

12.1 INSTITUTIONAL REVIEW BOARD (IRB)/RESEARCH ETHICS BOARD (REB)

The study protocol, protocol amendments, informed consent forms, and other relevant documents (e.g., recruitment advertisements) will be reviewed and approved by the IRB/REB prior to site initiation. All correspondence with the IRB/REB should be retained in the site's trial file with copies of IRB/REB communications forwarded to the Sponsor.

A protocol amendment may be implemented prior to IRB/REB approval only where the change is necessary to eliminate apparent immediate hazards to the participants. Should this occur, the investigator must notify the IRB/REB and the Sponsor in writing immediately after the implementation of the protocol amendment. No deviations to the protocol are permissible except when necessary to eliminate an immediate hazard to study participants. The investigator shall notify the IRB/REB of deviations from the protocol or serious adverse events occurring at the site, in accordance with local procedures.

12.2 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the *Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Participants*, adopted by the General Assembly of the World Medical Association (2013).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on *Good Clinical Practice*, and applicable local regulatory requirements and laws.

12.3 SUBJECT INFORMATION AND CONSENT

Informed consent will be administered in accordance with the requirements of 21 CFR 50.20-27, FDR C.05.010 and ICH E6 4.8, Principles of Good Clinical Practice, as applicable. Before protocol-specified procedures are carried out, the PI and study staff will explain the objectives of the study, study procedures, as well as

the risks involved to the study participant, his/her legally authorized representative (if applicable) and caregiver/informant prior to their inclusion in the trial.

Prior to performing any study-specific procedure, each study participant and the participant's caregiver/informant will be required to read and voluntarily sign an Institutional Review Board (IRB)/Research Ethics Board (REB) - approved informed consent form (ICF), indicating his/her consent to participate (or assent [where this is in accordance with local laws, regulations and ethics committee policy] in the case of participants who are deemed to be unable to have the cognitive ability to provide consent). This ICF will conform to the requirements of the applicable 21 CFR 50.20-27, FDR C.05.010 and ICH E6 Principles of Good Clinical Practice (GCP). The Study Sponsor must agree with the final IRB/REB-approved ICF prior to initiation of the study. Study participants will be provided adequate time to review the ICF and if they wish, may take it home to discuss their participation in the study with friends, family, and/or a physician. The original signed ICFs must remain in the study participant's file in the Study Site. Study participant will receive a copy of their signed ICF.

Continued consent / assent will be evaluated at each study visit for the duration of the study.

13.0 STUDY TERMINATION CRITERIA

The study may be terminated prematurely as a result of a regulatory authority decision, IRB/REB decision, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of azeliragon at any time.

Should the study be prematurely terminated, the Sponsor will promptly notify the investigator. Following notification, the investigator must contact all participating participants and the hospital pharmacy (if applicable) within 30 days.

14.0 CONFIDENTIALITY AND PUBLICATION OF STUDY RESULTS

The information in this and related documents from the Study Sponsor contains trade secrets and commercial information that are confidential and may not be disclosed unless such disclosure is required by federal or other laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Individual study participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the study participant's personal physician or to other appropriate medical personnel responsible for the study participant's welfare.

Data generated as a result of this study are to be available for inspection on request of the Sponsor's representative, the IRB/REB, or the local regulatory agency.

None of the parties involved in the management/conduct/analysis of this study may publish any study-related data without the written permission of the Study Sponsor.

No patent application based on the results of the study may be made by the PI, nor may assistance be given to any third party to make such an application, without the written authorization of the Study Sponsor. Publication of study results is discussed in the Clinical Study Agreement.

15.0 REFERENCES

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APPENDICES

APPENDIX 1

CRITERIA FOR SAFETY VALUES OF POTENTIAL CLINICAL CONCERN

vTv Therapeutics LLC
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Criteria for Safety Values of Potential Clinical Concern

Hematology

Assay	Lower limit of the normal reference range (LLN)	Upper limit of the normal reference range (ULN)
Hemoglobin	<0.8 times	>1.2 times
Hematocrit	<0.8 times	>1.2 times
RBC	<0.8 times	
Platelets	<0.5 times	>1.75 times
WBC	<0.6 times	>1.5 times
Total Neutrophils (abs)	<0.8 times	>1.2 times
Eosinophils (abs)		>1.2 times
Monocytes (abs)		>1.2 times
Basophils (abs)		>1.2 times
Lymphocytes (abs)	<0.8 times	>1.2 times

Chemistry

Assay	Lower limit of the normal reference range (LLN)	Upper limit of the normal reference range (ULN)
Total bilirubin		>1.5 times
AST		>3 times
ALT		>3 times
GGT		>3.0 times
Alkaline Phosphatase		>3.0 times
Creatinine		>1.5 times
BUN		>1.3 times
Glucose	<0.6 times	>1.5 times
Uric acid		>1.5 times
Sodium	<0.95 times	>1.05 times
Potassium	<0.9 times	>1.1 times
Calcium	<0.9 times	>1.1 times
Albumin	<0.8 times	>1.2 times
Total protein	<0.8 times	>1.2 times
Bicarbonate	<0.9 times	>1.1 times
Chloride	<0.9 times	>1.1 times

APPENDIX 2

PROHIBITED MEDICATION LIST

vTv Therapeutics LLC
4170 Mendenhall Oaks Pkwy
High Point, NC 27265

Prohibited Medication List

The following medications are NOT ALLOWED as concomitant medications during the study. The list is not exhaustive and therefore, the Investigator is asked to contact the Medical Monitor and/or the Sponsor for clarification regarding the acceptability of similar agents not mentioned here.

Drugs known to be strong CYP 2C8 inhibitors: NOT ALLOWED
gemfibrozil
clopidogrel

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "http://medicine.iupui.edu/clinpharm/ddis/clinical-table/" Accessed 17 Nov 2017.

Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry *DRAFT GUIDANCE*. October 2017.