vTv THERAPEUTICS LLC
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TITLE PAGE

CLINICAL TRIAL PROTOCOL

RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTI-CENTER REGISTRATION TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF TTP488 IN PATIENTS WITH MILD ALZHEIMER'S DISEASE RECEIVING ACETYLCHOLINESTERASE INHIBITORS AND/OR MEMANTINE

Investigational Product:	**TTP488**
Investigational Product Name:	**Azeliragon**
US IND Number:	**68,445**
Health Canada File Number:	**9427-T1538-21C**
EudraCT Number:	**2016-002005-19**
Protocol and Study Number:	**TTP488-301**
Clinical Phase:	**Phase 3**
Version and Date:	**AMENDMENT 7** **28 NOVEMBER 2017**

SIGNATURE CONFIRMATION PAGE

Investigational Product: **Azeliragon** (TTP488)

Study Number: TTP488-301

Protocol Title: **RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTI-CENTER REGISTRATION TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF TTP488 IN PATIENTS WITH MILD ALZHEIMER'S DISEASE RECEIVING ACETYLCHOLINESTERASE INHIBITORS AND/OR MEMANTINE**

Protocol Dated: **Amendment** 7 dated **28 NOVEMBER 2017**

I have reviewed and approved of the protocol listed above.

Dr. Larry Altstiel, M.D., Ph.D. 28 Nov 2017

Executive Vice President, Chief Medical Officer — Signature — Date
vTv Therapeutics LLC

Imogene Dunn, Ph.D. Imogene Dunn 28 NOV 2017

Senior Vice President, Biometrics and Regulatory Affairs — Signature — Date
vTv Therapeutics LLC

Aaron Burstein, Pharm.D. 29 NOV 2017

Senior Vice President, Clinical Development — Signature — Date
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Document Revision History

Document	Version Date	Summary of Changes
Amendment 7	28 NOV 2017	• Table 1 Removed dosing from the list of study procedures to be completed at the Month 18 visit. Added Early Termination PET to be consistent with Section 6.2.11. • Section 4.2 Exclusion Criteria ○ 19. Removed exclusion for participants who are taking or are expected to use drugs known to be strong CYP3A4 inhibitors. • Section 4.3. Added male contraceptive advice for fertile sexually active males to align with UK and IRL protocols. • Section 5.5. Removed CYP3A4 inhibitors from list of prohibited conmeds. • Section 6.2.9. Removed dosing from the list of study procedures to be completed at the Month 18 visit. • Section 6.2.10. Added description of when a Follow-up Visit should be performed (i.e., 3 months after Month 18 or 3 months after last dose when a subject discontinues early). • Section 6.3. Modified Early Termination Visit procedures to perform neuropsychological assessments only if the visit is within 30 days of the last dose of study drug. Added reference to follow-up visit performed 3-months after the last dose when a subject discontinues early. • Section 6.4. Added reference to follow-up visit for subjects who withdraw early. • Section 7.6. Modified MRI analyses to be unblinded to time sequence. • Section 7.8. Modified PET analyses to be unblinded to time sequence. • Section 8.4. Clarified that adverse event assessment of relationship to study drug falls into one of two categories: related / not related. • Section 11.1. Added cross reference to eCRF Completion Guidelines. • Appendix 2. Modified Prohibited Medication List to remove CYP3A4 inhibitors, and update list of strong CYP2C8 inhibitors based on updated references.
Amendment 6-UK (United Kingdom)	28 Sep 2016	• Title Page. Addition of Health Canada file number and EudraCT number. • Section 1.1.3. Presentation of TTP488-203 data

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Amendment 6	15 Jun 2016	revised to include mild subgroup (MMSE21-26) analysis. • Section 4.2. Exclusion criterion 20 removed based on the completed concentration-QTc analysis showing no deleterious effect of azeliragon on QT at therapeutic and supratherapeutic doses. • Section 5.3.2. Dosage instructions added for clarity. • Section 5.5. Removed restriction for drugs known to significantly increase QTc based on completed concentration-QTc analysis showing no deleterious effect of azeliragon on QT at therapeutic and supratherapeutic doses. • Section 9.12. Removed restrictions of materials to be provided to the IDMC, thereby giving liberty to the IDMC to request any material needed to review accruing data for safety evaluation. • Appendix 2. Revised to remove list of prohibited drugs known to significantly increase QTc.
Amendment 5-UK (United Kingdom)	08 July 2016	• Section 4.3. Inclusion of contraception advice for fertile sexually active males for submission to MHRA.
Amendment 5	23 Mar 2016	• Sections 4.1, 6.1, and 12.3. Clarified that the assent process is only applicable where it is in accordance with local laws, regulations and ethics committee policy. • Section 4.1. Modified inclusion criterion 11 to allow acetylcholinesterase inhibitors and memantine approved by any regulatory authority. • Section 4.2. Clarified application of exclusion criterion 25 regarding QTc values at screening and baseline visits. • Sections 5.5, 6.0, 6.2.1, 6.2.7, 6.2.9, 6.3, 7.8, and 9.1. Clarified that the FDG-PET substudy is being performed only at select sites in the United States and Canada. • Section 7.1.5.2. Clarified the abnormal laboratory values that elicit further evaluation as potential cases of drug-induced liver injury. Specifically, for sub-item “b” inclusion of text defining the bilirubin value to provide consistency with the definition provided in sub-item “a”. • Sections 9.12 and 9.13. In compliance with requests from the IDMC, vTv will provide safety tables only (no efficacy) for the IDMC to review for which the data tables represent subjects split into treatment

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		groups labeled "X" and "Y".
Amendment 4	30 Sep 2015	• Replacement of TransTech Pharma with vTv Therapeutics LLC • Revision of plan for assignment of sites to Study A and Study B. • Table 1, Section 6.1. Revised Screening Confirmation Form to Eligibility Assessment Form to reflect actual name of form in use. • Table 1. Clarification of allowable window for completion of baseline procedures and timing of baseline procedures relative to randomization and dosing. Added footnote "e" to clarify intention for first dose (Month 0) to be administered in the clinic following the completion of Baseline procedures. • Exclusion criteria o Clarification of Exclusion Criterion 2 allowing individuals from families with any number of late onset AD affected family members to participate in the study. o Clarification of Exclusion Criterion 5 to include ≥10 microhemmorrhages and grade 3 white matter changes as exclusionary. o Clarification of Exclusion Criterion 14 to reflect screening test is for drugs of abuse and does not include alcohol. o Revision of Exclusion Criterion 18 (and Section 5.5) to differentiate between prior investigational disease modifying, non-disease modifying, and active immunotherapy exposures. o Revision of Exclusion Criterion 20 to remove "with limited use" allowances for some prohibited concomitant medications. o Clarification of application of Exclusion Criterion 25. Also added allowances for participants with bundle branch block or functioning pacemaker. o Clarification of Exclusion Criterion 26 with regard to subjects with atrial fibrillation on anticoagulant therapy. • Section 5.1. Revision of randomization scheme to reflect that it will be blocked by substudy and investigative site. • Section 5.1. Clarification that stratification will be based on ADAS-cog assessed at the Screening visit.

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		• Sections 5.3.2, 6.2.2. Clarification that the first dose of study medication will be administered in the clinic at the conclusion of the Baseline visit. • Section 5.5. Revised instructions related to Pre-medication for PET assessment to be consistent with the PET Manual. Removed allowances for limited use of some prohibited concomitant medications. Clarified transient use of medications that may affect the CNS or cognition as no more than 4 weeks in duration. • Section 6.0, 6.1. Clarification of the order of cognitive / functional assessments at the Screening Visit to be consistent throughout protocol. Clarified dosing should occur in the clinic on study visit days. • Section 6.1. Added circumstances where re-screening is permitted. • Section 6.2.1. Clarification of allowable window for completion of baseline procedures and timing of baseline procedures relative to randomization and dosing • Section 6.3. Added FDG-PET assessment at Early Termination for those subjects participating in the PET sub-study who were on study for ≥ 3 months. • Section 7.1.2. Clarification of the application of Criterion 25 for participants with bundle branch block or functioning pacemaker. • Section 7.1.5.1. Clarified that serum FSH will be measured for all female subjects at Screening. • Section 7.2. Clarification of the order of cognitive / functional assessments at the Screening Visit to be consistent throughout protocol. • Section 7.7. Added reference to MRI procedures manual for instructions on submission of head CT scan. • Section 7.8. Revision to reflect that Baseline FDG-PET must be performed within the 7 days prior to the baseline visit. • Section 8.7.1. Revision to add Safety Monitor as the recipient of SAE reports and removed text regarding the separation of SAE report and AE CRF due to the use of a combined solution. • Section 9.0. Revision of the description of A-study and B-study to reflect assignment of the first approximately 400 patients to the A-study and the remaining approximately 400 patients to the B-study.

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		• Section 9.2. Addition of text to state specific statistical methodology for the MRI measures will be included in the SAP. • Section 9.5. Revision of the description of A-study and B-study to reflect assignment of the first approximately 400 patients to the A-study and the remaining approximately 400 patients to the B-study. • Section 9.14 and 11.1. Addition of description to clarify that the databases for each substudy (A-study and B-study) will be locked, unblinded, analyzed, and reported separately. • Appendix 2. Updated list of prohibited concomitant medications due to a known risk of Torsades de Pointe.
Amendment 3	31 Mar 2015	• Replacement of TTP488 with the INN name azeliragon • Change laboratory sample collections from fasting to non-fasted. • Addition of concomitant medication exclusion of prescription medical food (i.e. Axona) intended for the dietary management of the metabolic processes associated with Alzheimer's disease. • Clarify order of procedures (Section 6.0) with regard to timing of conduct of cognitive/functional/ behavioral assessments relative to other procedures • Clarification of the application of consistent exclusion criteria across the screening and baseline visit for QTc values. • Clarification that ECG performed in triplicate only at baseline visit and as single measures at all other time points. • Addition of the following text to Exclusion Criteria 18. Previous exposure to any other investigational drug as part of a clinical trial, including investigational therapies for Alzheimer's disease that are being investigated for non-disease modifying purposes, within 6 months prior to screening. • Clarification of exclusion criteria that unstable diabetes or requirement for insulin is exclusionary. • Clarification that a response of "yes" to items 4 and 5 on the C-SSRS at screening and baseline will result in subjects not being included in the study. • Elimination of the requirement of a healthy volunteer test scan for MRI QA/QC and a patient volunteers test scan for PET QA/QC. Scan of ACR and

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		Hoffman phantoms is required for monitoring of optimal scan parameters. • Allowance of computed tomography as an alternate imaging modality at screening for subjects with contraindications to MRI. Results of CT will be used to determine eligibility in trial. For those subjects using CT based qualification for study no Month 18 or Early Term MRI will be required.
Amendment 2	10 Feb 2015	• Addition of Trail Making Test (Versions A and B to the secondary endpoints and objectives) as a measure of executive function potentially sensitive to change in a patient with mild AD. Test to be performed at Baseline and Months 3, 6, 12, 18, Follow-up, and Early Termination (if applicable) Visits. • Clarification that RUD referred to the RUD Lite. Addition of "Lite" after each instance of word RUD • Elimination of Month 1 and Month 2 visits to clinic and replacing with Telephone Calls for assessment of Adverse Events and/or concomitant medication changes. Subjects may be brought into clinic for unplanned study visit based on information obtained from telephone calls. Change results in 9 outpatient visits including Screening and Follow-up. • Addition of ADAS-cog and CDR to screening visit. The ADAS-cog at screening will be used as a stratification variable in the randomization scheme. • Brain MRI eliminated at Months 6 and 12 in response to letter from FDA eliminating the need for MRIs for evaluation of ARIA with small molecules • Update of Abbreviations to include C-SSRS, MMA, and NASH • Description of staff members (PI, Coordinator, Rater, CDR Rater) and clarification of the instruments he/she may be permitted to administer. • Inclusion Criteria – Modification of language to describe legally authorized representative, caregiver/informant instead of caregiver – Modification of MMSE criteria to specify needs to be within 21-26 at Screening. Elimination of requirement for value to be within range at baseline visit – Addition of CDR global score of 0.5 or 1

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		– Item 12. Addition of text "If the results of clinical laboratory testing are outside normal reference ranges, the subject may be enrolled but only if these findings are determined to be not clinically significant by the investigator. This determination must be recorded in the subject's source documents. • Exclusion Criteria – Item 1. Addition of text "proximate to the onset of dementia, participation in contact sports characterized by repeated head injuries" and "current major depression, bipolar disorder, alcohol or substance abuse or dependence, neurosyphilis, vitamin B12 deficiency (see Exclusion 3, below), thyroid disease (unless adequately treated for at least 3 months with normalization of laboratory values) or any form of dementia other than AD.". – Item 5. Elimination of text describing specific findings on MRI that would result in exclusion from trial because the MRI requirements for inclusion in the trial are adequately addressed in Inclusion Criteria 7. – Elimination of Item 8. Clinically significant depression as determined by scores on the NPI depression domain. Original intent was that this itself does not warrant exclusion but rather is used in evaluation of suicidality risk and as trigger for risk assessment by qualified health care professional. Amendment now bases evaluation of suicidality risk solely on C-SSRS. – Item 8. Addition of "or cervical carcinoma in-situ" – Item 9. Increase BMI cutoff to 35 kg/m2 – Item 11. Modified to clarify criteria "Patients with unstable, uncontrolled diabetes and those with insulin dependent diabetes mellitus" – Item 15. Modified to clarify criteria. Intent was not to exclude "Participants with mild chronic pulmonary disease which has been stable on treatment without hospitalization or emergency room treatment for 2 years." – Item 18. Modified to clarify intent to be "Previous exposure to investigational therapies for Alzheimer's disease that are being investigated for possible disease modification

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		activity (e.g., TTP488, immunotherapies and secretase inhibitors) within 6 months of screening for the current protocol." – Elimination of former Item 24 "participants cannot participate in other clinical drug trials or other nondrug methodology trials for the duration of the study." Other drug trials covered under Item 18. Non-drug trials permitted. – Item 24. QTc criteria updated to exclude QTcF>470 msec for females and >450 msec for males. • Section 5.2 Addition of text "The sponsor or representative should be consulted prior to breaking the blind except in emergent circumstances." • Section 5.3.3 Addition of text "Caregivers/Informants will be instructed to assist with monitoring dosing compliance." • Section 5.5 Concomitant Medications: Section added to clarify that "Considerations for use of medications that may affect the CNS or cognition. 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, 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 with a view to discontinuing the subject from participation." Elimination of text "Participants may receive medication that may negatively affect cognitive function (e.g., sedatives/anxiolytics, antipsychotics) only if used to manage transient fluctuation in mental status (e.g., confusion due to UTI or transient insomnia). All such cases need to be discussed and approved by the Sponsor's medical monitor and documented in source documentation. Such medications may not be introduced for chronic usage to manage chronic deterioration of the subject's mental status due to disease progression. Participants who need to start a behavioral medication or need to change the dose of a

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		behavioral medication during the study should be on a stable dose for at least one week prior to any clinical assessments." Exclusion of grapefruit and grapefruit juice • Section 6.0 Study Procedures: – Updating to reflect changes previously described above – Addition of text "Note, the initial rating scales should be the ADAS-cog to minimize subject fatigue, followed by the MMSE. Additionally, to avoid subject fatigue, it is recommended that the CDR is performed on a separate visit day than the other cognitive tests. If it is to be done the same day, then the CDR should follow the MMSE as above. The exception to this is the Screening visit during which the MMSE will be performed first, followed by the ADAS-cog and CDR if the subject is eligible based on their MMSE score." – Elimination of allowance of up to 90 days from MRI to dosing. Only time this will be permitted is in the event of rescreening a subject – Rescreening a subject will be permitted for "Hypertension discovered at screening that is subsequently actively managed and the blood pressure values are within acceptable limits" – Addition of a review of drug accountability at each visit to study site. – Vitamin B12 level revised to 211 to reflect LabCorp reference value. • Section 7.1.2 Addition of text "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." • Section 7.1.5.2 Addition of text requiring Medical Monitor be contacted to discuss patient condition • Section 7.2.1 Addition of text to describe the Trail Making Tests • Section 7.3 Elimination of the NPI depression domain as part of the evaluation of potential suicidality risk. Risk evaluation will be based on the C-SSRS • Section 7.4. Update title of section to reflect that plasma will be collected for analysis of TTP488 and

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		metabolites. Correction of inconsistency in sample collection times. Reduction of sample volume from 5 mL to 4 mL. Text includes statement "For TTP488 metabolites, samples may be analyzed at the Sponsor's discretion." • Section 7.6 Intent is that MRI will be centrally read with results of central reader being definitive result. Section of text describing baseline scans being read by neuroradiologist at site within 48 hours removed. • Section 7.9 Section updated to correct inconsistency of sampling times across protocol. Sample storage conditions updated to -70°C. • Section 7.10 Blood volume: updated to eliminate redundant sampling for exploratory biomarkers and removal of Month 1 labs. • Section 8.6: redundant text regarding follow-up for ongoing adverse events deleted • Section 9.12 updated to reflect intent to have at least 3 members on IDMC • Section 12.3 updated to include text "(or assent in the case of participants who are deemed to be unable to have the cognitive ability to provide consent)."
Amendment 1 (Canada)	16 Dec 2014	Addition of country-specific language and references for submission to Health Canada.
Original Protocol	21 Jan 2014	N/A

PROTOCOL SUMMARY

Background and Rationale:

Azeliragon (TTP488) is an orally bioavailable antagonist of Receptor for Advanced Glycation Endproducts (RAGE) that is being developed as a potential treatment for AD.

Substantial data suggest that RAGE is involved in the pathogenesis of AD, and that sustained Aβ interaction with RAGE on blood brain barrier (BBB) and/or neuronal cells and/or microglial cells is an important element of amyloid plaque formation and chronic neuronal dysfunction. The non-clinical and clinical data obtained to date indicate that azeliragon plus standard of care (SoC), at 5 mg/day, is well tolerated in humans and results in statistically significant differences (Δ=3.1, $p<0.008$) from placebo plus SoC in change in ADAS-cog after 18 months of treatment. Thus, azeliragon has the potential to provide effective treatment of AD.

Objectives:

The primary objective of this study is:

- To evaluate the efficacy of azeliragon on cognitive [Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)] and global function [Clinical Dementia Rating Scale Sum of Boxes (CDR-sb)] measures in patients with mild AD.

The secondary objectives of this study are:

Key Secondary

- To examine the effect of azeliragon on MRI volumetrics (e.g., whole brain volume, ventricular volume, hippocampal volume).
    * note: the decision as to the specific key secondary to support disease modification claim will be made prior to database lock.

Secondary:

- To evaluate the safety and tolerability of 18 months treatment with azeliragon plus standard of care relative to placebo plus standard of care.
- To evaluate the time course of the effect of azeliragon on the cognitive (ADAS-cog) and global functional outcome (CDR-sb) measures.

- To evaluate the efficacy of azeliragon on behavioral symptoms as assessed by the Neuropsychiatric Inventory (NPI).

- To evaluate the efficacy of azeliragon on cognition as assessed by the Mini-Mental State Examination (MMSE).

- To evaluate the efficacy of azeliragon on the Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale (ADCS-ADL).

- To evaluate the efficacy of azeliragon on cognition as assessed by the Continuous Oral Word Association Task (COWAT), Category Fluency Test (CFT) and Trail Making Test (Versions A and B).

- To evaluate the effect of azeliragon on health status, health care resource utilization, and health-related quality of life as assessed by Resource Utilization in Dementia (RUD Lite), and Dementia Quality of Life (DEMQOL-proxy)

- To evaluate the effect of azeliragon on regional and global brain glucose metabolism using FDG-PET.

- To evaluate the effect of azeliragon on plasma Aβ biomarkers.

- To evaluate azeliragon exposure-response relationships for selected efficacy, safety and biomarker endpoints (e.g., ADAS-cog, ADCS-ADL, adverse events, vital signs, plasma concentrations of Aβ).

Endpoints:

Primary Endpoints:

Co-primary Endpoints:

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

Secondary Endpoints:

Key Secondary Endpoints:

- Change from Baseline in brain volumetrics (e.g., whole brain volume, ventricular volume, hippocampal volume) at Month 18.

Other Secondary Endpoints:

- Adverse events, clinical safety laboratory tests, MRI, ECG, vital signs.
- Responder analysis at Months 6, 12 and 18 based on the ADAS-cog.
- Responder analysis at Months 6, 12 and 18 based on the CDR-sb.
- The slope of change over time in ADAS-cog, MMSE and CDR-sb scales through Month 18.
- Time to loss of one global stage on the CDR score through Month 18.
- Proportion of participants experiencing a loss of one global stage on the CDR global score at Months 6, 12, and 18.
- Change from Baseline on the ADAS-cog and CDR-sb total scores at Months 6 and 12.
- Change from Baseline in the ADCS-ADL total score at Months 6, 12 and 18.
- Change from Baseline in the NPI total score at Months 3, 6, 12 and 18.
- Change from Baseline in the MMSE total score at Months 3, 6, 12 and 18.
- Change from Baseline in the COWAT and CFT score at Months 3, 6, 12 and 18.
- Change from Baseline in Trail making Test (versions A and B) time at Months 3, 6, 12 and 18.
- Individual item responses on the RUD Lite questionnaire and the total caregiver/informant time spent assisting the patients based on the RUD Lite questionnaire at Months 6, 12 and 18.
- Proportion of participants who enter intermediate or long-term residential care (RUD Lite).
- Change from Baseline in the DEMQOL-proxy total score at Month 18.
- Change from Baseline in regional and global brain glucose metabolism using FDG- PET at Month 18
- Change from Baseline in plasma concentrations of Aβ species at Month 18.

- Exposure response relationships based on selected efficacy, safety, and biomarker outcomes.

Study Design:

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of 18 months of treatment with azeliragon relative to placebo conducted in approximately 800 mild AD patients who are on background SoC. Patients will be randomly assigned to 1 dose level (5 mg/day) or placebo in a 1:1 randomization (approximately n=400/group).

Statistics:

This protocol describes two studies with a common infrastructure. Statistical analysis for clinical efficacy will be analyzed as 2 separate studies. Analysis for safety and for imaging data will be analyzed as one study as a whole.

Sample Size and Randomization

A total of approximately 800 patients will be randomized into this study. Subjects will be enrolled and randomized according to a fixed randomization scheme blocked by study investigative site. Severity of AD will be determined by MMSE (21-26) at screening. ADAS-cog at Screening will be used as a stratification variable in the randomization scheme:

- ADAS-cog 19 or less
- ADAS-cog more than 19.

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

This study comprises two studies in one main study for purposes of independent replication for the co-primary variables: A-study is composed of the first approximately 400 patients randomized; B-study is composed of the remaining approximately 400 patients. Each A-study and B-study is powered independently and is expected to randomize approximately N=400 patients (each).

Sample size calculations are done to power each study (A-study and B-study) separately. It is anticipated that each A-study and B-study will randomize approximately N=400 each.

Assuming a standard deviation of the change from Baseline to Month 18 in ADAS-cog of 9 (based on Study TTP488-203), using alpha = 0.05, a total sample size of 282 patients in balanced allocation (141 patients per group) provides at least 90% power to detect a difference between treatment groups of 3.5 (based on data from mild AD patients in Study TTP488-203) using a 2-sided, 2-sample t-test. Assuming a dropout rate of 20% or less, randomization of 354 patients provides adequate statistical power for this study to demonstrate superiority of azeliragon plus SoC over placebo plus SoC based on the ADAS-cog.

Assuming a standard deviation of the change from Baseline to Month 18 in CDR-sb of 2.4, using alpha = 0.05, a total sample size of 304 patients in balanced allocation (152 patients per group) provides at least 90% power to detect a difference between treatment groups of 0.9 (based on data from mild AD patients in Study TTP488-203) using a 2-sided, 2-sample t-test. Assuming a dropout rate of 20% or less, randomization of 380 patients provides adequate statistical power for this study to demonstrate superiority of azeliragon plus SoC over placebo plus SoC based on CDR-sb.

For purposes of increased exposure in the study, a total of 800 AD patients are planned for this study.

Populations 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 excluding subjects who have major protocol violations.
- 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.

Efficacy Analysis

For inferential purposes, each (independent) study A-study and B-study) will be analyzed separately for the co-primary variables. The study as a whole will be analyzed for specified inferential purposes.

A 2-stage conditional sequence of statistical hypothesis tests, will be used. The testing sequence will be as follows:

- Stage 1: 4 concurrent analyses will be done:
  - A-study analysis of co-primary variables:
    - ADAS-cog is analyzed in A-Study.
    - CDR-sb is analyzed in A-Study
  - B-study analysis of co-primary variables:
    - ADAS-cog is analyzed in B-study.
    - CDR-sb is analyzed in B-study
- Stage 2: Conditional on statistical significance of both A-study and B-study in both co-primary variables, testing will continue:
  - MRI assessment is analyzed in the study (as a whole).

The primary analysis will use the intent-to-treat (ITT) methodology and a main-effects model for mixed-models repeated measures (MMRM) analysis with adjustment for baseline ADAS-cog (CDR-sb) measures. The primary analysis will be supported by multiple-imputation methods, also with last-observation-carried-forward (LOCF) methods, and also an observed cases analysis (no imputation, no deletion). The primary MMRM analysis will include treatment, time and treatment-by-time interaction as fixed effects, baseline as covariate, baseline stratum as a covariate, and subject as a random effect. Supportive modeling will also include MMRM main-effects model with treatment, time, and subject.

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 plus SoC.

SCHEDULE OF ACTIVITIES

Table 1. Schedule of Activities

Protocol Activity	Screening	Baseline	Treatment									Early Term	Follow-up[a]
	Day -60 to Day -1	Day -7 to Day 1	Month 0	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18		Month 21
Study Days			1	30	60	90	180	270	360	450	540		630
Window			±4d	±4d	±4d	±7d	±7d	±7d	±7d	±7d	±7d		± 7d
Sign informed consent / provide assent[f]	X												
Eligibility Assessment Form (EAF)[b]	X												
Registration/Randomization		X											
Demographic information	X												
Review Inclusion/Exclusion Criteria	X	X											
Medical History	X												
Drug, Alcohol, Tobacco Use History	X												
Complete Neuro Exam & Physical Exam	X												
Rosen-Modified Hachinski Ischemic Score	X												
Height	X												
ApoE genotyping		X											
Telephone contact				X	X								
Body weight	X	X				X	X	X	X	X	X	X	
Brief Neuro & Physical Exams		X				X	X	X	X	X	X	X	X
Review Concomitant Medications	X	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	X
12 Lead ECG[d]	X	X				X	X	X	X	X	X	X	X
Adverse Events Assessment		X		X	X	X	X	X	X	X	X	X	X
Dispense Study Drug		X				X	X	X	X	X			

Table 1. Schedule of Activities (continued)

Protocol Activity	Screening	Baseline	Treatment									Early Term	Follow-up[a]
	Day -60 to Day -1	Day -7 to Day 1	Month 0	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18		Month 21
Study Days			1	30	60	90	180	270	360	450	540		630
Window			±4d	±4d	±4d	±7d	±7d	±7d	±7d	±7d	±7d		± 7d
Study Drug Dosing[e]			X	→	→	→	→	→	→	→			
MMSE	X	X				X	X		X		X	X[h]	X
ADAS-cog	X	X				X	X	X	X	X	X	X[h]	X
CDR	X	X				X	X		X		X	X[h]	X
NPI		X				X	X		X		X	X[h]	X
ADCS-ADL		X				X	X		X		X	X[h]	X
COWAT		X				X	X		X		X	X[h]	X
CFT		X				X	X		X		X	X[h]	X
Trail Making Test (Versions A and B)		X				X	X		X		X	X[h]	X
Columbia Suicide Severity Scale (C-SSRS)[c]	X	X				X	X	X	X	X	X	X	X
RUD Lite		X					X		X		X	X[h]	
DEMQOL-proxy		X					X		X		X	X[h]	
FSH (females only), hepatitis, VDRL, Thyroid function tests, Vitamin B12	X												
Hematology	X	X				X	X	X	X	X	X	X	X
Blood Chemistry (incl HbA1c)	X	X				X	X	X	X	X	X	X	X
Urinalysis	X	X				X	X	X	X	X	X	X	X
Urine Drug Screen	X												
Brain MRI	X										X	X	
Brain CT (for subjects with contraindications to MRI)	X												
Brain FDG-PET[g]		X							X		X	X	

Table 1. Schedule of Activities (continued)

Protocol Activity	Screening	Baseline	Treatment									Early Term	Follow-up[a]
	Day -60 to Day -1	Day -7 to Day 1	Month 0	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18		Month 21
Blood Sample for Plasma Retention and Storage		X				X	X		X		X	X	X
Pharmacokinetic Blood Sampling		X				X	X		X		X	X	X
Pharmacodynamic blood sampling (Aβ)		X				X	X		X		X	X	X

a Follow-up visit required for those participants completing the study but choosing to not participate in an open label extension study.
b Following completion of Screening visit assessments but prior to scheduling baseline visit, obtain approval from the sponsor for the patient to participate in the study.
c C-SSRS is administered to subject jointly with care-giver.
d ECGs at Baseline visit performed in triplicate
e First dose (Month 0) in the clinic following baseline visit procedures.
f Where assent is in accordance with local laws, regulations and ethics committee policy
g Only applicable at select sites in the United States and Canada.
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.

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LIST OF ABBREVIATIONS

Aβ	Aβ peptide fragment of the amyloid precursor protein
Aβ (1–40)	1–40 amino acids of Aβ
Aβ (1–42)	1–42 amino acids of Aβ
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive measure
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living scale
ADL	Activities of Daily Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRDA	Alzheimer's Disease and Related Disorders Association
AE	Adverse Event
AGE	Advanced Glycation Endproduct
ALT	Alanine Aminotransferase
APP	Amyloid Precursor Protein
AST	Aspartate Aminotransferase
BBB	Blood Brain Barrier
β-hCG	β-Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale-Sum of Boxes
CFT	Category Fluency Test
COWAT	Continuous Oral Word Association Task
CPK	Creatine Phosphokinase
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed Tomography
DEMQOL	Health-Related Quality of Life for People with Dementia
IDMC	Independent Data Monitoring Committee
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th ed Text Revision
ECG	Electrocardiogram
FAS	Full analysis set
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Methylmalonic Acid
MMSE	Mini-Mental State Exam
MRI	Magnetic Resonance Imaging
NASH	Nonalcoholic Steatohepatitis
NIA	National Institute on Aging
NINCDS	National Institute of Neurological Communicative Disorders and Stroke
NPI	Neuropsychiatric Inventory Questionnaire
PD	Pharmacodynamic
PET	Positron Emission Tomography

LIST OF ABBREVIATIONS (continued)

PI	Principal Investigator
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
sRAGE	Soluble Form of Receptor for Advanced Glycation Endproducts
TEAE	Treatment-Emergent Adverse Event
TEAV	Treatment-Emergent Abnormal Value
TSH	Thyroid Stimulating Hormone
TTP488	Azeliragon
ULN	Upper Limit of Normal
QD	Taken Once Daily
QoL	Quality of Life
QTcB	QT interval calculated using Bazett's correction factor
QTcF	QT interval calculated using Fridericia's correction factor
WHO	World Health Organization
WHODD	WHO Drug Dictionary

1.0 INTRODUCTION

This Phase 3 study is designed to evaluate the efficacy and safety of azeliragon (TTP488) in participants with mild Alzheimer's disease (AD).

1.1 BACKGROUND AND RATIONALE

1.1.1 Alzheimer's Disease

Alzheimer disease (AD) is a neurodegenerative disorder characterized by progressive loss of memory and cognitive function. AD is the most common form of dementia, is currently estimated to afflict approximately 5.4 million people in the United States and represents the 6th leading cause of death. Worldwide there are currently 35.6 million people with dementia, and the number is expected to double by the year 2050. (Alzheimer's Association 2012)

1.1.2 Mechanism of Action

Azeliragon is an orally bioavailable antagonist of the Receptor for Advanced Glycation Endproducts (RAGE) that is being developed as a potential treatment for AD.

An overproduction of amyloid beta (Aβ) has been implicated as the leading mechanistic factor in AD pathology. Aβ is known to bind to RAGE, an immunoglobulin supergene family member expressed on multiple cell types in the brain and the periphery (Yan et al., 1996; Schmidt et al., 2009). RAGE is found on the cells of the neurovascular compartment: endothelial cells and microglia prominently express RAGE whose expression is upregulated in AD (Yan et al., 2007; Yan et al, 2009). RAGE ligands include Aβ, S100b, HMGB1, and Advanced Glycation Endproducts. RAGE-ligand interactions lead to sustained inflammatory states that play a role in chronic diseases such as diabetes, inflammation, and AD (Stern et al., 2002; Bierhaus et al., 2005). RAGE has been proposed to contribute to AD pathology by: promoting vascular leakage, promoting influx of peripheral Aβ into brain; mediating Aβ-induced oxidative stress and Aβ-mediated neuronal death (Deane et al., 2003; Carrano et al., 2011; Hartz et al., 2012; Kook et al., 2012).

The pleiotropic role of RAGE in AD pathology has been described using rodent models. Mice expressing the human amyloid precursor protein (APP) transgene in neurons develop significant biochemical and behavioral changes reminiscent of human AD. Double transgenic mouse overexpressing wild type RAGE in the APP transgene background exhibit accelerated behavioral changes, whereas double transgenic animals expressing a dominant negative mutant of RAGE are protected (Arancio et al., 2004). This data suggests that RAGE plays a role in augmenting the chronic inflammatory state caused by overproduction of Aβ.

RAGE is thought to be involved in the transport of Aβ from peripheral to central nervous system compartments (Tanzi et al., 2004). In vivo, Aβ uptake into brain is dependent on RAGE as shown in RAGE null mice (Deane et al., 2003). Similarly, Aβ uptake in brain can be inhibited using either the secreted, soluble form of RAGE (called sRAGE) or an anti- RAGE antibody (Deane et al., 2003). In addition, plaque formation in a mouse model of cerebral amyloidosis was inhibited using sRAGE (Yan et al., 2000; Rocken et al., 2003). These data suggest that RAGE is intimately involved in the pathogenesis of AD, and that sustained Aβ interaction with RAGE on blood-brain barrier and/or neuronal cells is an important element of amyloid plaque formation and chronic neuronal dysfunction.

1.1.3 Clinical Studies

A summary of the Phase 1 program and the 10-week Phase 2 safety study in patients with mild-to-moderate AD is provided in the Investigator's Brochure. In addition a 6 months study of azeliragon in 110 patients with Type 2 diabetes and persistent albuminuria and an 18 month study of azeliragon in 399 patients with mild to moderate Alzheimer's disease have been completed.

The first study of chronic administration of azeliragon as a treatment for AD was TTP488-203, a Phase 2, double-blind, placebo-controlled, randomized, multicenter study evaluating the efficacy and safety of 18 months of treatment with azeliragon. The study was conducted in 399 participants diagnosed with mild to moderate AD with a Mini-Mental State Exam (MMSE; score between 14-26). Participants were randomized 1:1:1 to one of 2 dose regimens of azeliragon or placebo and dosed with investigational drug every morning for 18 months. Treatment began on the baseline

visit with 60 mg/day for 6 days and 20 mg/day thereafter, 15 mg/day for 6 days and 5 mg/day thereafter, or placebo once daily in the morning with food for 18 months.

Study visits occurred at screening, baseline, then at 4 weeks, 3, 6, 9, 12, 15, and 18 months, with a safety follow-up visit at 21 months. Visits included clinical and safety evaluations, blood draw for plasma biomarker and PK analysis, and pill counts to assess compliance. Brain MRIs (using standard Alzheimer's Disease Neuroimaging Initiative [ADNI] acquisition parameters) were obtained at baseline, 12 and 18 months.

The primary efficacy measure was the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog). The ADAS-cog/12-item scale (Scored 0-80) was administered before the first dose, and at 3, 6, 9, 12, 15, and 18 months with the prespecified analyses being on the ADAS-cog/11-item scale (Scored 0-70). Primary safety measures included reports of AEs, blood and urine tests, and ECG measures.

Secondary clinical measures included the Clinical Dementia Rating - Sum of Boxes (CDR- sb) (key secondary); Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale (ADCS-ADL), Neuropsychiatric Inventory (NPI) and MMSE. These were administered prior to dosing and at Months 6, 12, and 18.

Blood samples for azeliragon PK analysis were collected prior to dosing at Week 1, at Months 1, 3, 6, 9, 12, 15, 18, and 21, and at Early Termination.

Three interim analyses were planned during the study. The first interim analysis was conducted 6 months after approximately 50% of participants had been randomized. This analysis was conducted for the purposes of safety and for informing internal development decisions. The second interim analysis was conducted 12 months after all participants were randomized to assess futility, as well as for safety and to inform internal development decisions. A third interim analysis to inform internal development decisions was to be conducted when all continuing participants completed the Month 18 visit.

The first pre-specified interim safety analysis revealed an increased frequency of AEs (concentration related and reversible upon discontinuation of treatment), in particular falls and confusion, in the 20 mg/day group relative to the 5 mg/day and

placebo groups. This was associated with a higher percentage of participants in the 20 mg/day group declining by ≥10 points on the ADAS-cog (relative to Baseline scores) at Months 3 and 6 (concentration related and stabilized/reversible upon discontinuation of treatment). These findings were not noted for the 5 mg/day group or the placebo group. On the recommendation of the Data and Safety Monitoring Board (IDMC), participants randomized to the 20-mg/day dose discontinued study drug, received a safety evaluation, and were asked to consent to continue to be followed for safety clinical and laboratory assessments.

Approximately 12 months after all participants were randomized, the second pre-specified interim analysis compared 5 mg/day and placebo for futility based on results of the completer population (i.e. those with available 18-month ADAS-cog data) Conditional power was computed based on assumed continuation of the observed trend.

While safety data raised no concerns, criterion for futility (<10% conditional power to observe a significant difference between 5 mg/day and placebo at 18 months) was met and treatment was discontinued. The third interim analysis was not performed as the study was terminated due to futility. Attempts to replicate the futility analysis, using a data set representative of that which would have been used for the futility analysis (constructed from the final data set) have been unsuccessful with conditional probabilities consistently computed as >20%.

Upon completion of the study and locking the database, protocol-planned analysis of ADAS-cog data from 100% of subjects who were ongoing or who had completed 18 months at the time of study termination were performed. Analysis showed a beneficial effect of less cognitive decline in the 5 mg/day group compared to placebo at Month 18 (delta = 3.1, p = 0.008, analysis of covariance [ANCOVA] with multiple imputation). To confirm robustness of effect to statistical analysis procedures, this difference was found to be significant using other statistical models (ANCOVA with last observation carried forward [LOCF; p = 0.03] and generalized estimating equations [GEE; p = 0.03]).

Analysis was done to examine the impact of off-treatment data on analysis conclusions. Statistical analysis on ADAS-cog was performed using all available on-treatment data ("on treatment" defined as data collected within 45 days of the last

dose of study medication). Forty-five days was selected based on the long half-life of azeliragon (mean = 18 days in elderly participants) and the demonstration of measureable, appreciable concentrations during that time frame following the last dose. Mean changes in ADAS-cog show numerical active-placebo differences favoring the 5 mg/day dose group over time at all time points, with nominal significance at Month 18 (delta=2.7, p = 0.03).

The key secondary measure of CDR-sb at 18 months showed a numerical difference favoring 5 mg azeliragon over placebo CDR-sb (LOCF, delta = 0.73, p = 0.1)

The current study will enroll patients with mild Alzheimer's disease. Subgroup analyses of data in Study TTP488-203 based on baseline severity of AD (mild or moderate), planned in the protocol and SAP, showed a more pronounced benefit of treatment with azeliragon among subjects with mild disease (MMSE 21 or more). In patients with mild AD, the difference in ADAS-cog mean change from baseline at 18 months was 4.0 (p = 0.018). In addition, a nominally statistically significant difference in CDR-sb mean change from baseline was demonstrated (delta = 1, p = 0.02) when comparing azeliragon 5 mg + SoC with placebo + SoC at Month 18. Thus, in the Phase 2 trial statistically significant differences between azeliragon 5 mg/day and placebo on cognition and global performance (using USA FDA agreed upon Phase 3 registration measures of ADAS-cog and CDR-sb) have been demonstrated.

1.1.4 Dose Selection Rationale

The azeliragon dose (5 mg daily) for the registration studies 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).

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 2.

Table 2. 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 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.

Preliminary evaluation of the effect of food on the pharmacokinetics of azeliragon has been performed from data collected in the TTP488-101 and TTP488-102 studies. Comparison of dose normalized pharmacokinetics for data obtained from Study TTP488-101 (single, ascending doses administered under fasting conditions; 5, 10, 20, 35, 50, and 65 mg) and the first administered dose, under fed conditions, from Study TTP488-102 (multiple dose administration; 15, 30, 60, and 30 mg in elderly subjects) demonstrate up to an approximate

30% decrease in C_{max} and AUC_{0-24} when administered in the fed state. This magnitude of difference in PK between fed and fasted state is not anticipated to be clinically meaningful for subjects dosed with 5 mg/d (anticipated concentration 8 to 15 ng/mL fasted; 10 to 20 ng/mL fed) as concentrations will be within the range associated with efficacy in TTP488-203 and well below those associated with the acute, reversible cognitive worsening in the 20 mg/d group (>47 ng/mL).

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

Primary objective:

- To evaluate the efficacy of azeliragon on cognitive [Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)] and global function [Clinical Dementia Rating Scale Sum of Boxes (CDR-sb)] measures in patients with mild AD.

Key secondary objective:

- To examine the effect of azeliragon on MRI volumetrics (e.g., whole brain volume, ventricular volume, hippocampal volume).
  * note: the decision as to the specific key secondary to support disease modification claim will be made prior to database lock.

Secondary objectives:

- To evaluate the safety and tolerability of 18 months treatment with azeliragon plus standard of care relative to placebo plus standard of care.
- To evaluate the time course of the effect of azeliragon on the cognitive (ADAS-cog) and global functional outcome (CDR-sb) measures.
- To evaluate the efficacy of azeliragon on behavioral symptoms as assessed by the Neuropsychiatric Inventory (NPI).
- To evaluate the efficacy of azeliragon on cognitive symptoms as assessed by the Mini-Mental State Examination (MMSE).
- To evaluate the efficacy of azeliragon on the Alzheimer’s Disease Cooperative Study - Activities of Daily Living Scale (ADCS-ADL).
- To evaluate the efficacy of azeliragon on cognition as assessed by the Continuous Oral Word Association Task (COWAT), Category Fluency Test (CFT) and Trail Making Test (Versions A and B).

- To evaluate the effect of azeliragon on health status, health care resource utilization, and health-related quality of life as assessed by Resource Utilization in Dementia (RUD Lite), and Dementia Quality of Life (DEMQOL-proxy).
- To evaluate the effect of azeliragon on regional and global brain glucose metabolism using FDG-PET.
- To evaluate the effect of azeliragon on plasma Aβ biomarkers.
- To evaluate exposure-response relationships for selected efficacy and biomarker endpoints (e.g., ADAS-cog, ADCS-ADL, adverse events, vital signs).

2.2 ENDPOINTS

Primary Endpoint (Co-primary endpoints):

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

Key Secondary Endpoints:

- Change from Baseline in brain volumetrics (e.g., whole brain volume, ventricular volume, hippocampal volume) at Month 18

Other Secondary Endpoints:

- Adverse events, clinical safety laboratory tests, MRI, ECG, vital signs.
- Responder analysis at Months 6, 12 and 18 based on the ADAS-cog.
- Responder analysis at Months 6, 12 and 18 based on the CDR-sb.
- The slope of change over time in ADAS-cog, MMSE and CDR-sb scales through Month 18.
- Time to loss of one global stage on the CDR score through Month 18.
- Proportion of participants experiencing a loss of one global stage on the CDR global score at Months 6, 12, and 18.

- Change from Baseline on the ADAS-cog and CDR-sb total scores at Months 6 and 12.
- Change from Baseline in the ADCS-ADL total score at Months 6, 12 and 18.
- Change from Baseline in the NPI total score at Months 3, 6, 12 and 18.
- Change from Baseline in the MMSE total score at Months 3, 6, 12 and 18.
- Change from Baseline in the COWAT and CFT score at Months 3, 6, 12 and 18.
- Change from Baseline in Trail Making Test (versions A and B) time at Months 3, 6, 12 and 18.
- Individual item responses on the RUD Lite questionnaire and the total caregiver/informant time spent assisting the patients based on the RUD Lite questionnaire at Months 6, 12 and 18.
- Proportion of participants who enter intermediate or long-term residential care (RUD Lite).
- Change from Baseline in the DEMQOL-proxy total score at Month 18.
- Change from Baseline in regional and global brain glucose metabolism using FDG- PET at Month 18
- Change from Baseline in plasma concentrations of Aβ species at Month 18.
- Exposure response relationships based on selected efficacy, safety, and biomarker outcomes.

3.0 STUDY DESIGN

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of 18 months of treatment with azeliragon relative to placebo. The study will be conducted in approximately 800 patients diagnosed with mild AD (MMSE 21-26) who are on background SoC. Participants will be randomly assigned one dose of azeliragon (5 mg/day plus SoC) or placebo plus SoC in a 1:1 randomization (approximately n=400/group). Randomization will be stratified based on severity of disease and will be blocked by substudy (A-Study and B-Study), and randomization will be blocked by investigative site. Approximately 160 of these subjects will be targeted for participation in FDG-PET.

Participants are required to be on SoC of a stable background (defined as at least 3 months on a consistent dose prior to randomization) acetylcholinesterase inhibitor therapy and continue the therapy for the duration of the trial, unless the investigator judges that the dose needs to be reduced or stopped due to a safety and/or tolerability reason. Participants on memantine similarly must be on a stable dose for at least 3 months prior to randomization and continue therapy for the duration of the trial unless the investigator judges that the dose needs to be reduced or stopped due to a safety and/or tolerability reason.

Behavioral medications (including antidepressants, antipsychotics and anxiolytics) must be on stable doses for at least 4 weeks prior to randomization. In the case where a behavioral medication is initiated during the trial, at least one week period at a stable dose must elapse before clinical assessments are obtained.

Subject will participate in approximately 9 outpatient visits including screening and follow up visit.

A minimum of three staff members will be required to conduct the protocol at each site. Details will be provided in the procedures manual.

- Principal Investigator (PI) – This person is responsible for the clinical evaluation of all participants, ensuring enrollment and protocol adherence, endpoint determinations, and decisions regarding breaking the blind. The PI

will supervise project personnel and ensure that raters maintain a high level of skill and accuracy in conducting assessments.

- 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, but may not perform the CDR-SB if s/he is responsible for study oversight.

- Rater – This person will have at least a bachelor's degree in health care psychology, social work or a related field, or be an RN and meet the clinical and scale experience requirements set by TTP. This person can conduct all ratings and assessments.

- CDR Rater – This person will render the CDR-SB rating based on clinical assessment of participant and study partner, using worksheets provided by the Sponsor, but without access to the ADAS-cog. Since the CDR-SB is a co-primary endpoint with the ADAS-cog, it is important for the CDR rater to remain blinded to ADAS-cog data and all other scales for that subject.

4.0 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

Subject eligibility should 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 assent (where this is in accordance with local laws, regulations and ethics committee policy) and assent may be re-evaluated during the study at regular intervals.

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

3. 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. Caregivers/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, in particular the CDR 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.

4. 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.

5. Males and females (of non-childbearing potential) ages ≥50 years of age at screening.

6. Diagnosis of probable AD, consistent with the criteria from the 2011 National Institute on Aging and the Alzheimer's Association workgroup (McKhann et al., 2011). Evidence of progression needs to 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). Biomarker evidence of the pathophysiological process or neuronal injury associated with AD should be documented if data is available in participant's medical records (not specifically measured for inclusion in this study).

7. MRI consistent with a diagnosis of probable Alzheimer's disease. A head CT scan may be used for evaluation if there is a documented contraindication to an MRI (e.g. pacemaker).

8. Mini-Mental State Exam (MMSE) score of 21-26 inclusive at screening.

9. CDR global score of 0.5 or 1 at screening.

10. Rosen-Modified Hachinski Ischemia Score ≤4 at screening.

11. Participants must be on a stable dose of a background cholinesterase inhibitor and/or memantine (approved by the relevant health authority where the trial is being conducted) at least 3 months prior to randomization and must agree not to change the 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.

12. No clinically significant, (in the opinion of the investigator) laboratory abnormalities at screening. If the results of clinical laboratory testing are outside normal reference ranges, the subject may be enrolled but only if these findings are determined to be not clinically significant by the investigator. This determination must be recorded in the subject's source documents. A summary of values of potential clinical concern is provided in APPENDIX 1.

13. 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, psychiatric, and any other illness that could contribute to dementia including, but not limited to other neurodegenerative disorders (e.g., Lewy body disease, fronto-temporal dementia, vascular dementia), head injury with loss of consciousness proximate to the onset of dementia, participation in contact sports characterized by repeated head injuries, DSM-IV-TR criteria for any major psychiatric disorder including psychosis, current major depression, bipolar disorder, alcohol or substance abuse or dependence, neurosyphilis, vitamin B12 deficiency (see Exclusion 3, below), thyroid disease (unless adequately treated for at least 3 months with normalization of laboratory values) or any form of dementia other than AD.

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. Diagnosis or 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 an 18-month 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 18-month course of the trial. In any case, 10 or more microhemorrhages as identified by the central reading, is exclusionary. Grade three deep white matter changes (diffuse involvement of entire region) on the central reading report is exclusionary. If a head CT is used for assessment of eligibility, structural abnormalities 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 18-month course of the trial would be exclusionary.

6. A current primary diagnosis of major psychiatric disorder, e.g., schizophrenia, bipolar disorder, major depressive disorder, or other severe psychiatric illness per the DSM-IV-TR criteria per the investigator's judgment.

7. Serious suicide risk per the following criteria:

   - 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 or,
   - 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 or,
   - Lifetime history of serious or recurrent suicidal behavior.

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 treatment.

9. Current (e.g., within the last 3 months) body mass index (BMI) of greater than or equal to 35 kg/m2 or a current (e.g., within the last 3 months) weight less than 45 kg.

10. Any clinically significant hepatic or renal disease, elevated transaminase levels of greater than 1.5 times the upper limit of normal (ULN), creatinine greater than 1.5 x ULN.

11. Patients with unstable, uncontrolled diabetes (HbA1c > 7.7%) and those requiring insulin.

12. Participants with poorly controlled hypertension with or without existing therapy (systolic≥160 or diastolic≥100). Subjects 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.

13. 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.

14. Known history of alcohol or drug abuse or dependence (as defined by the DSM-IV-TR) within 5 years prior to dosing or a positive result on the drug screening test (unless due to a permitted concomitant medication (i.e., a benzodiazepine as a sleep aid).

15. Patients with pulmonary hypertension are excluded.

16. Any contraindications to the MRI procedure based on local operating procedures and instructions (e.g., clinically significant claustrophobia, non-removable ferromagnetic implants). It is acceptable to premedicate patients per usual local practice provided this medication is not administered within 5 half-lives preceding any efficacy assessments. Patients with contraindications to MRI (ex: pacemakers) may undergo computed tomography (CT) on approval by Sponsor.

17. Any contraindications to the FDG-PET study (e.g. allergy to any component of the FDG dose) in the mild AD dementia subject cohort undergoing a PET scan.

18. Previous exposure to investigational therapies for Alzheimer's disease that are being investigated for possible disease modification activity (e.g., azeliragon, passive immunotherapies and secretase inhibitors) within 4 months of screening for the current protocol. Subjects who were exposed to vaccine therapy or other active immunization (if they were randomized to active treatment) will not be allowed in the trial. Previous exposure to any other investigational drug as part of a clinical trial, including investigational therapies

for Alzheimer's disease that are being investigated for non-disease modifying purposes, within 60 days or 5 half-lives whichever is longer, prior to screening.

19. Participants who are taking or are expected to use drugs known to be strong CYP2C8 inhibitors or (See APPENDIX 2 for a list of such medications).

20. 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.

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

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

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

24. Subjects demonstrating a QTcF > 470 msec for females or > 450 msec for males on the screening ECG, as confirmed by the central reading. If the average of three locally read ECGs performed at baseline exceeds these values, then a determination of the subject's eligibility will be delayed until the baseline QTcF result is obtained from the central reading. If the average of the three centrally read values exceeds 470 msec for females or 450 msec for males, the subject will not be randomized. Subjects with an average of three locally read ECGs performed at baseline ≤470 msec for females or ≤450 msec for males will be randomized. For these randomized subjects, if the baseline average QTcF on the central reading of the ECG subsequently is > 470 msec for females or > 450 msec for males, the sponsor's medical monitor will be consulted for a determination regarding the acceptability of continued dosing with study medication. Participants with known history of bundle branch block (either right or left) are allowed if absolute QTcF value does not exceed 500 ms.

Participants with a functioning pacemaker, indicated by an ECG displaying paced rhythm, are allowed with no QTc upper limit.

25. History of clinically significant cardiac disease as determined by the PI and in consultation with the Sponsor. Examples of cardiac disease that would be unlikely to allow study enrollment 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.

26. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may prevent the subject from completing the 18-month study or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial.

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.

5.0 STUDY TREATMENTS

5.1 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 substudy (A-Study and B-Study will be randomized separately) and study investigative site. Severity of AD will be determined by MMSE at screening. ADAS-cog at Screening will be used as a stratification variable in the randomization scheme:

- ADAS-cog 19 or less.
- ADAS-cog more than 19.

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

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

5.2 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 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 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, as long as all study procedures have been completed and the subject is deemed qualified to randomize and has been randomized and assigned drug. 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 18-month treatment period. The day's dose of study medication will be administered in the clinic at 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.

5.4 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.

5.5 CONCOMITANT MEDICATION(S)

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

Participants must be on a stable dose of background cholinesterase inhibitor and/or memantine at least 3 months prior to dosing. Dose reductions of background cholinesterase inhibitor and/or memantine 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 are not permitted during the course of the trial.

Medications taken within 60 days prior to screening must be documented as a prior medication. All past medications/therapies for Alzheimer's disease must be recorded. Medications taken after the first dose of study medication must be documented as concomitant medications.

Medications that may negatively affect cognitive function (e.g., antidepressants, 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 should 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.

- Participants should not receive pre-medication (e.g. sedative for anxiolytic) for the PET assessment (PET substudy applies only for select sites in the US and Canada).

- 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 with a view to discontinuing the subject from participation.

The use of following concomitant medications is not allowed:

- Drugs known to be potent 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 Alzheimer's disease that are being investigated for possible disease modification activity (e.g., azeliragon, passive immunotherapies and secretase inhibitors) within 4 months of screening for the current protocol.

No investigational therapies that are being investigated for non-disease modifying purposes, within 60 days or 5 half-lives whichever is longer, prior to screening.

Subjects who were exposed to vaccine therapy or other active immunization (if they were randomized to active treatment) will not be allowed in the trial.

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 medications should be approved by the investigator prior to use and recorded on the Case Report Form (CRF). If the medication is started because of an adverse event (AE), this event should be reported on the appropriate CRF.

Any additional questions regarding medications should be addressed to the Sponsor's medical monitor.

6.0 STUDY PROCEDURES

- Study participants should consume a meal or snack prior to their clinic visit. Upon arrival, the Site staff will confirm the subject has consumed a meal or snack prior to beginning study procedures. The time of the finishing the meal/snack will be documented in the source documents. Thus clinical laboratories will be obtained under non-fasting conditions at all visits.

- Cognitive/functional assessments (in particular the ADAS-cog, MMSE and CDR-sb) should be performed as first procedures during a study visit.

- It is recommended that cognitive/functional assessments should be performed in the following order: ADAS-cog, MMSE, 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. Note, the initial rating scales should be the ADAS-cog to minimize subject fatigue, followed by the MMSE. Additionally, to avoid subject fatigue, the CDR may be performed on a separate visit day than the other cognitive tests. If it is to be done the same day, then the CDR should follow the MMSE as above. The exception to this is the Screening visit during which the MMSE will be performed first. If the subject is eligible based on their MMSE score, proceed with the remaining screening assessments.

- Following completion of the cognitive/functional assessments the remainder of study visit procedures will be completed.

- ECGs: obtain prior to blood sampling. Obtain in triplicate at baseline visit and as single tracings at all other study days.

- Vital signs: obtain prior to blood sampling.

- Blood sampling should be the last procedure performed prior to dosing during a study visit.

- Dosing should occur in the clinic on study visit days.

- Patient blood glucose level should be assessed immediately prior to administration of the FDG-PET dose (for those subjects participating in the PET substudy). This blood sample may be fasting or non-fasting.

6.1 SCREENING

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 where 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.

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.
- Complete MMSE to determine subject eligibility. If subject is eligible based on the MMSE, proceed with the remainder of screening visit in any order.
- ADAS-Cog
- The Columbia Suicide Severity Scale (C-SSRS)
- CDR (calculation of both global score and sum of boxes score global)
- Demographic information (i.e., sex, date of birth, race/ethnicity).
- Complete medical and surgical history, including family medical history of dementia.
- 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.
- Rosen-Modified Hachinski Ischemia Scale
- Height and body weight.
- Vital signs: blood pressure (supine), pulse rate.
- Single 12-lead electrocardiogram (ECG).
- Review of inclusion and exclusion criteria.
- Blood and urine specimens for safety laboratory tests (serum chemistry, hematology, UA) will be collected, in addition to the following:
  - Serum glucose and HbA1c;
  - Hepatitis screens (including hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, and hepatitis C antibody);
  - Syphilis test. If positive, a standard confirmation test will be obtained;
  - Thyroid function (T3, T4, and TSH);
  - Vitamin B12 (and MMA if indicated, e.g., if serum B12 level <211 pg/mL);
  - Serum FSH concentrations in all female participants to confirm post-menopausal status and eligibility regarding non-child bearing potential;
  - Urine drug screen.
- Brain MRI performed at least 14 days prior to Month 0/Day 1 dosing; 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.
- Upon completion of screening procedures, and prior to the Baseline visit, approval from the Sponsor on the Eligibility Assessment Form (EAF) must be obtained before proceeding to the Baseline visit.

Re-screening of a Participant

Participants previously screened but not dosed in another AD study, including a azeliragon study may participate in this study provided they meet the subject selection criteria. All screening data must be obtained within 60 days prior to the first dose of study medication.

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

- 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 acetylcholinesterase inhibitors or/and memantine for at least 3 months prior to planned dosing may rescreen once they have reached 3 months of stable dosing of acetylcholinesterase inhibitors or/and memantine.

- Participants excluded because of potentially undiagnosed type 2 diabetes, provided that their disease and serum glucose values are now controlled and being actively managed, per the investigator's judgment.

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

- Subjects who have a CDR of 0 or an MMSE score >26 may rescreen upon approval of the sponsor’s medical monitor. CDR 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.

6.2 STUDY PERIOD

6.2.1 Baseline (approximately Day -7-Day 1)

- ADAS-cog, MMSE, CDR-sb, ADCS-ADL, COWAT, CFT, Trail Making Test (Versions A and B), NPI, RUD Lite, DEMQOL-proxy
- C-SSRS.
- Review of inclusion and exclusion criteria including the results of the MRI scan.
- Brief physical and neurologic examination.
- Update concomitant medications.
- Weight.
- Assess baseline symptoms/adverse events.
- 12-lead electrocardiogram (ECG) (performed in triplicate).
- Vital signs: blood pressure (supine), pulse rate.
- Baseline FDG-PET (if applicable).
- 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.
- Randomize subject if eligible.
- Dispense study drug if eligible.
- Subject begins taking study medication in the clinic as soon as baseline procedures are completed (noted as Month 0 [Day 1] on Table 1. Schedule of Activities).

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 will remain in effect. Should the overall screening time exceed 60 days, re-screening will be required.

6.2.2 Month 1 (± 4 days)

- Telephone contact.
- 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 Month 2 (± 4 days)

- Telephone contact.
- Review and record new concomitant medications.
- Assess symptoms/adverse events and 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?"

6.2.4 Month 3 (± 7 days)

- ADAS-cog, MMSE, CDR, ADCS-ADL, COWAT, CFT and Trail making test (Versions A and B), and NPI.
- 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.
- ECG.
- Vital signs: blood pressure (supine) and pulse rate.
- Collect blood sample for plasma retention and storage.
- Blood and urine sampling for safety laboratory testing including HbA1c.
- Collect blood samples for PK and PD.
- 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 dose of study medication in the clinic.

6.2.5 Month 6 (± 7 days)

- ADAS-cog, MMSE, CDR, ADCS-ADL, COWAT, CFT, Trail making test (Versions A and B), NPI, RUD Lite and DEMQOL- proxy.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events and 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.
- ECG.
- Vital signs: blood pressure (supine) and pulse rate.
- Collect blood sample for plasma retention and storage.
- Blood and urine sampling for safety laboratory testing including HbA1c.

- Collect blood samples for PK and PD
- 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 dose of study medication in the clinic.

6.2.6 Month 9 (± 7 days)

- ADAS-cog.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events and 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.
- ECG.
- Vital signs: blood pressure (supine) and pulse rate.
- Blood and urine sampling for safety laboratory testing including HbA1c.
- 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 dose of study medication in the clinic.

6.2.7 Month 12 (± 7 days)

- ADAS-cog, MMSE, CDR, ADCS-ADL, COWAT, CFT, Trail making test (Versions A and B), NPI, RUD Lite and DEMQOL- proxy.
- C-SSRS.
- Review and record new concomitant medications.

- Assess symptoms/adverse events and 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.
- ECG.
- Vital signs: blood pressure (supine) and pulse rate.
- FDG-PET (if applicable)
- Collect blood sample for plasma retention and storage.
- Blood and urine sampling for safety laboratory testing including HbA1c.
- Collect blood samples for PK and PD.
- 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 dose of study medication in the clinic.

6.2.8 Month 15 (± 7 days)

- ADAS-cog.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events and 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.
- ECG.
- Vital signs: blood pressure (supine) and pulse rate.
- Blood and urine sampling for safety laboratory testing including HbA1c.

- 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 dose of study medication in the clinic.

6.2.9 Month 18 (± 7 days)

- ADAS-cog, MMSE, CDR, ADCS-ADL, COWAT, CFT, Trail making test (Versions A and B), NPI, RUD Lite and DEMQOL- proxy.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events and 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.
- ECG.
- Vital signs: blood pressure (supine) and pulse rate.
- MRI if one was obtained during the screening period. If a CT scan was used for assessing eligibility, then the 18 month MRI scan will not be performed, and the CT scan will not be repeated.
- FDG-PET (if applicable).
- Collect blood sample for plasma retention and storage.
- Blood and urine sampling for safety laboratory testing including HbA1c.
- Collect blood samples for PK and PD.
- Drug accountability. Any discrepancies are recorded in the source and the subject and caregiver/informant are counseled regarding proper dosing compliance.

6.2.10 Follow-Up

A Follow-up Visit should be completed 3 months [±7 days] after a subject completes Month 18 for those participants who choose not to participate in the open label extension.

A follow-up Visit should be completed 3 months [±7 days] after the last dose of study drug if the subjects 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.

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

- ADAS-cog, MMSE, CDR, ADCS-ADL COWAT, CFT, Trail making test (Versions A and B), and NPI.
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events and by asking the participants to respond to a non-leading question such as “How have you been feeling?”
- Brief physical and neurologic examination.
- ECG.
- Vital signs: blood pressure (supine) and pulse rate.
- Collect blood sample for plasma retention and storage.
- Blood and urine sampling for safety laboratory testing including HbA1c.
- Collect blood samples for PK and PD.

6.3 EARLY TERMINATION

In the event a subject discontinues participation prior to completion of the Month 18 Visit, the Early Termination Visit should be completed performing the study procedures as follows. A Follow-up Visit should be performed 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.

- ADAS-cog, MMSE, CDR, ADCS-ADL, COWAT, CFT, Trail Making Tests (Versions A and B), NPI, RUD Lite and DEMQOL- proxy. (These neuropsychological assessments are only performed at the Early Termination visit if within 30 days of the last dose of study drug)
- C-SSRS.
- Review and record new concomitant medications.
- Assess symptoms/adverse events and 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.
- ECG.
- Vital signs: blood pressure (supine) and pulse rate.
- MRI if one was obtained during the screening period. If a CT scan was used for assessing eligibility, then this MRI scan will not be performed and a CT scan will not be performed at this visit.
- FDG-PET if participant was on study for ≥ 3 months (if applicable) and if an MRI scan has been performed and passed the central reader's quality control review. In all cases, it should only be performed if the subject was taking study drug at the time of the PET scan.
- Collect blood sample for plasma retention and storage.
- Blood and urine sampling for safety laboratory testing including HbA1c.
- Collect blood samples for PK and PD.
- Drug accountability. Any discrepancies are recorded in the source.

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 an Early Termination and Follow-up Visit and follow-up with the participant regarding any unresolved adverse events.

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 into the follow-up period) 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 in the study will be sufficient reason for participant discontinuation from 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, brain MRI and neuropsychological testing batteries.

7.0 ASSESSMENTS

7.1 SAFETY AND TOLERABILITY

7.1.1 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.

7.1.2 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 ms and the subject does not have any other cardiac exclusions as described in exclusion criterion 26. When an ECG displays a paced rhythm indicating a functioning pacemaker is present, there is no upper limit as long as there are no related cardiac exclusions (reference exclusion criterion 26). 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 >450 msec for males or >470 msec for females 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.

7.1.3 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. A brief physical examination will be conducted at all the study visits. Body weight will be also examined at all study visits.

7.1.4 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.

7.1.5 Laboratory

7.1.5.1 Standard Safety Laboratory Tests

Unless noted otherwise, the following safety laboratory tests will be performed at Screening, Baseline, Month 3, 6, 9, 12, 15, 18, 21 and at time of premature discontinuation. All routine laboratory tests will be analyzed by a central laboratory which 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 Glucose Calcium Sodium Potassium Chloride Total CO2 (Bicarbonate) AST ALT GGT LDH Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein HbA1c	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy[a]	FSH[b] Urine drug screen T3, T4, TSH Vitamin B12 Syphilis 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.

7.1.5.2 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. Participants should not have initiated treatment with a behavioral medication within 1 week of next clinical assessment. If there is any condition that, in the opinion of the investigator, may jeopardize the accurate evaluation of participant's function, participants should not receive neuropsychological tests, and reserve an additional visit to evaluate function within the allowance of the visit window. Neuropsychological assessments should not be performed if the patient is fasting. The same rater should follow a particular participant for any given assessment for the duration of the study whenever possible. It is recommended that the scales be administered in the following order if they are specified to occur at the same visit: ADAS-cog, MMSE, CDR, ADCS-ADL, COWAT, CFT, Trail Making Test (Versions A and B), NPI, RUD Lite, and DEMQOL. The exception to this is the Screening visit during which the MMSE will be performed first. If the subject is eligible proceed with the remainder of screening visit in any order.

The CDR may be performed at a separate visit. For the Baseline and Month 18 visits, the CDR may be done on a separate proximal visit day to avoid patient fatigue if feasible. It is acceptable for the CDR, ADCS-ADL, and the NPI to be performed together on a separate visit day from the other cognitive assessments. All cognitive assessments must be performed by a trained rater.

7.2.1 Cognitive Assessments

<u>Alzheimer's Disease Assessment Scale - Cognitive Subscale 70 point (ADAS-cog):</u>

The ADAS-cog is a structured scale (approximately 40 minutes to complete) that evaluates memory, orientation, attention, reasoning, language and constructional praxis (Rosen, 1984). The ADAS-cog scoring range for the version used in this study is from 0 to 70, with higher scores indicating greater cognitive impairment. The ADAS-cog will be conducted at Screening, Baseline and at Months 3, 6, 9, 12, 15, 18, and 21 or in the event of early termination. The ADAS-cog should always be administered prior to other cognitive measures.

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 at Screening, Baseline, and at Months 3, 6, 12, 18, and 21 or in the event of early termination. Scores range from 0-30 with lower scores indicating greater cognitive impairment. Participants with scores of 21-26 will be eligible for participation in the study.

Controlled Oral Word Association Test (COWAT): The COWAT is a measure of verbal fluency in which the participant is asked to generate orally as many words as possible that begin with the letters "F", "A", and "S", excluding proper names and different forms of the same word. (Borkowski, 1967, Loonstra 2001) For each letter, the participant is allowed one minute to generate the words. Performance is measured by the total number of correct words produced summed across the three letters. Perseverations (i.e., repetitions of a correct word) and intrusions (i.e., words not beginning with the designated letter) are noted.

Although fluency tests are sensitive to language dysfunction and deterioration of semantic knowledge, they can also reflect an inability to initiate systematic retrieval of information in semantic storage. The COWAT will be administered at Baseline, and at Months 3, 6, 12, 18, and 21 or in the event of early termination.

Category fluency test (CFT): Study participants are given one minute to provide exemplars of the category 'animals'. The CFT will be administered at Baseline, and at Months 3, 6, 12, 18, and 21 or in the event of early termination.

Trail Making Test, Parts A and B: (from the Halstead Reitan Neuropsychological Test Battery; Reitan, 1958). Part A consists of 25 circles numbered 1 through 25 semi-randomly distributed over a white sheet of 8 1/2" X 11" paper. The participant is instructed to connect the circles with a pencil line as quickly as possible in ascending numerical order. Part B also consists of 25 circles, but these circles are either numbered (1 through 13) or contain letters (A through L). Now the participant must connect the circles while alternating between numbers and letters in an ascending order (eg, A to 1; 1 to B; B to 2; 2 to C). Trails A and B are available in multiple forms of equal difficulty for purposes of repeated evaluations. The participant's performance can be judged in terms of the time (in seconds) required to complete each trail and by the number of errors of commission and omission. The time to complete Trails A (150 second maximum) and B (300 second maximum) will be the measures of interest. Whereas both Trails A and B depend on attention, visuomotor, and perceptual scanning skills, Trails B also requires considerable flexibility in shifting from number to letter sets under time pressure. Thus, participants who perseverate their current response set will encounter special difficulty with Trails B. The Trail Making Test (Parts A and B) will be administered at Baseline, and at Months 3, 6, 12, 18, and 21 or in the event of early termination.

7.2.2 Functional/Global Assessments

Alzheimer's Disease Cooperative Study Activities of Daily Living Scale(ADCS-ADL): The ADCS-ADL is an activity of daily living inventory developed by the ADCS to assess functional performance in participants with AD (Galasko et al., 1997). Informants are queried via a structured interview format as to whether participants attempted each item in the inventory during the preceding 4 weeks, as well as their level of performance. The ADCS-ADL will be administered at Baseline, and at Months 3, 6, 12, 18, and 21 or in the event of early termination. Scores range from 0-78 with lower scores indicating greater functional impairment.

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 patient and caregiver (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. Much of the information

will therefore already have been gathered, either as part of normal clinical practice or as part of a research study. The interview takes approximately 40 minutes to administer.

CDR ratings are 0 for healthy 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 (CSR-SB). Sum of box scores range from 0 to 18 with higher scores indicating greater cognitive impairment.

The CDR will be conducted at Screening, Baseline and at Months 3, 6, 12, 18, and 21 or in the event of early termination. CDR should be done on a separate proximal visit day to avoid patient fatigue if feasible, particularly at baseline and Month 18.

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 et al, 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 at Screening, Baseline, and at Months 3, 6, 12, 18, and 21 or in the event of early termination.

Resource Utilization in Dementia (RUD Lite): The RUD Lite is a validated and reliable questionnaire which assesses the health care resource utilization (HCRU) of the patient and caregiver and measures the level of formal and informal care

(Wimo et al, 2012). The RUD Lite consists of items about caregiver time, caregiver work status, caregiver HCRU (e.g., hospitalization, ER visits, health care professional visits and medication), patient living accommodation, and patient HCRU. It takes approximately 15-20 minutes to complete and is usually interview administered by any health care professional. This scale will be administered at Baseline and at Months 6, 12 and 18 or in the event of early termination.

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 et al, 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 Baseline and at Months 6, 12 and 18 or in the event of early termination.

Rosen-Modified Hachinski Ischemia Score: this brief rating scale is used to assess if dementia could be attributed to vascular causes (Rosen et al., 1984). The scale ranges from 0-18 with higher scores indicating a greater presence of vascular risk factors. Dementia is not likely to be due to vascular causes if the score is 4 or less. This scale is only performed at Screening Visit to rule out vascular dementia.

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 et al, 2011). This scale will be administered at Screening Visit to evaluate life time suicide attempt, suicide behaviors, and other non-suicidal self-injuries. 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.

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 should 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 a 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. A change from baseline to a yes on any of these items will also constitute an AE and will be documented as such.

7.4 PLASMA FOR ANALYSIS OF AZELIRAGON AND METABOLITE CONCENTRATIONS

Blood samples for pharmacokinetic analysis will be collected prior to dosing at Baseline, Months 3, 6, 12, 18 and 21 or at Early Termination.

Blood samples (4 mL) to provide plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing dipotassium (K2) EDTA at times specified above.

Samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C within 1 hour of collection.

For azeliragon metabolites, samples may be analyzed at the Sponsor's discretion.

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 prior to dosing on Baseline, Months 3, 6, 12, 18, 21 or at Early Termination.

Blood samples for plasma biomarkers (6 mL for Aβ analysis) will be collected into appropriately labeled tubes containing dipotassium (K2) EDTA at times specified above.

Samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -70°C within 1 hour of collection. Instructions on collection, processing, storage and shipment of the sample will be provided in a separate laboratory manual.

7.6 MRI

MRI scans will be performed at Screening and Month 18 or in the event of early termination. 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 and to confirm the presence of hippocampal atrophy. The screening MRI must be performed at least 14 days prior to dosing to allow for the central read and interpretation of results prior to dosing. This brain MRI scan will also serve as the subject's baseline MRI for the study.

Specific MRI scan sequences for safety and volumetric assessments will be outlined in the MRI procedures manual. Participants will be monitored and data will be reacquired if there is subject movement during the scan. The data will be analyzed to determine any new clinical findings and atrophy of whole brain and hippocampus (as well as measurement of ventricular volume) to assess changes relative to baseline.

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 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 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 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.

Whole brain, ventricular, and hippocampal volumes will be computed at Screening and at Month 18. 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 and will not contribute to the MRI volumetric analyses.

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 FDG-PET

FDG-PET scans will be performed at Baseline and Months 12 and 18 or in the event of early termination in a mild AD dementia subset cohort at select sites in the United States and Canada. The Baseline FDG- PET scan must be performed within 7 days prior to the baseline visit and +/- 7 days at Months 12 and 18. A central analysis and read will be performed on all PET scans.

Specific FDG-PET acquisition, processing and display guidelines will be outlined in the PET Imaging Manual. A blood glucose level will be obtained immediately prior to the administration of the FDG-PET dose. The PET scans will be analyzed to determine any new clinical findings as well as extent and severity of regional and global brain glucose metabolism changes relative to Baseline.

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

Extent and severity of brain hypometabolism will be assessed centrally at Baseline, Months 12 and 18 by a neuro PET reader(s) who will be blinded to subject treatment.

7.9 APOE GENOTYPING

A 3 ml 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.

7.10 BLOOD SAMPLING FOR PLASMA STORAGE AND RETENTION

A 10 mL blood sample will be collected at Baseline and Months 3, 6, 12, 18, and 21 or Early Termination. Blood samples will be collected into appropriately labeled tubes containing dipotassium (K2) EDTA. Samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -70°C within 1 hour of collection.

Samples will be stored for potential future analysis for plasma biomarkers that may be identified during the course of the trial.

7.11 BLOOD VOLUME

Total blood sampling volume for the individual participants is approximately 264 mL.

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening / Baseline	Treatment	Non-treatment Follow-up	
Routine Laboratory	13	2	6	1	117
Unique Screening Labs	24	1	0	0	24
PK	4	1	4	1	24
Biomarkers (Aβ)	6	1	4	1	36
ApoE Genotyping	3	1	0	0	3
Plasma Storage and Retention	10	1	4	1	60
TOTAL (mL)					264

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 at Month 21. 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. 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

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.

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, or 60 days from end of study participation.

- All AEs with a relationship other than *not related* will be followed until resolution, 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 Safety Monitor. 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 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 the following subsection outline the 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 study. 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 with a common infrastructure in a single protocol. Statistical analysis of the clinical efficacy variables will be done for each of the studies separately. Statistical analysis of safety and imaging data 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 9.1 or later will be used. Medical dictionary for Regulatory Activities.

(MedDRA) Version 16.0 or later will be used for coding adverse events. Medications will be coded using WHO Drug Dictionary (WHODD) Version March 2009 or later.

This study is planned using an enrichment strategy, following the draft regulatory guidance depicted in the FDA guidance *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* (draft guidance, December, 2012). This study features a conditional sequential approach to hypothesis testing to control alpha, similar to methods using Bauer closed procedures, which are referenced in the FDA adaptive design guidance FDA guidance *Adaptive Design for Clinical Trials for Drugs and Biologics* (draft guidance, February 2010) referenced above), and principles for subgroup analyses.

This study comprises two independent sub-studies in one main study for purposes of independent replication for the co-primary variables: A-Study is composed of the first approximately 400 patients randomized; B-Study is composed of the remaining approximately 400 patients randomized. The study as a whole will be analyzed for specified inferential purposes. A-Study and B-Study will be randomized separately.

A 2-Stage conditional sequence of statistical hypothesis tests, will be used. The testing sequence will be as follows:

1. Stage 1: concurrent analyses for co-primaries in each of the two independent sub-studies:
   - ADAS-cog is analyzed in A-Study and B-Study independently.
   - CDR-sb is analyzed in A-Study and B-Study independently

2. Stage 2: conditional on significance in all of the first set of analyses:
   - MRI assessment is analyzed in the study (as a whole).

9.1 SAMPLE SIZE DETERMINATION

The primary objective is to evaluate the effect of azeliragon plus SoC on cognition and functional outcome by comparing azeliragon plus SoC with placebo plus SoC. The co-primary endpoints are change from Baseline on the ADAS-cog total score at Month 18 and change from Baseline on the CDR-sb total score at Month 18. The study includes AD patients with mild disease as defined by having a baseline MMSE of 21 through 26.

This trial includes two independent sub-studies, each of which is supported by randomization independently, because randomization by investigative site is used. Each sub-study is powered using alpha = 0.05.

Approximately 160 subjects (80 per treatment group) will be enrolled and participate in the FDG-PET sub-study at select sites in the United States and Canada. The sample size for this sub-study was selected empirically.

Sample size calculations are done to power each study (A-study and B-study) separately. It is anticipated that each A-study and B-study will randomize approximately N=400 each.

Assuming a standard deviation of the change from Baseline to Month 18 in ADAS-cog of 9 (based on Study TTP488-203), using alpha = 0.05, a total sample size of 282 patients in balanced allocation (141 patients per group) provides at least 90% power to detect a difference between treatment groups of 3.5 (based on data from mild AD patients in Study TTP488-203) using a 2-sided, 2-sample t-test. Assuming a dropout rate of 20% or less, randomization of 354 patients provides adequate statistical power for this study to demonstrate superiority of azeliragon plus SoC over placebo plus SoC based on the ADAS-cog.

Assuming a standard deviation of the change from Baseline to Month 18 in CDR-sb of 2.4, using alpha = 0.05, a total sample size of 304 patients in balanced allocation (152 patients per group) provides at least 90% power to detect a difference between treatment groups of 0.9 (based on data from mild AD patients in Study TTP488-203) using a 2-sided, 2-sample t-test. Assuming a dropout rate of 20% or less, randomization of 380 patients provides adequate statistical power for this study to demonstrate superiority of azeliragon plus SoC over placebo plus SoC based on CDR-sb.

9.2 STATISTICAL HYPOTHESES

A 2-stage conditional sequence of statistical hypothesis tests, will be used. The testing sequence will be as follows:

- Stage 1: 4 concurrent analyses will be done:
  - A-study analysis of co-primary variables:
    - ADAS-cog is analyzed in A-Study.
    - CDR-sb is analyzed in A-Study
  - B-study analysis of co-primary variables:
    - ADAS-cog is analyzed in B-study.
    - CDR-sb is analyzed in B-study

- Stage 2: Conditional on statistical significance of both A-study and B-study in both co- primary variables, testing will continue:
  - MRI assessment is analyzed in the study (as a whole).

For simplicity in notation, thresholds for significance are indicated as "$p<0.05$"; however, "0.05" is representative of the alpha allocated to the analysis. The overall study-wise alpha is 0.05, but particular analyses may have alpha less than 0.05. STAGE 1:

Hypothesis tests for A-study are as follows:

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

- H_{01}: μ(ADAS-cog, azeliragon, A-study)$=$ μ(ADAS-cog, P, A-study)
- H_{11}: μ(ADAS-cog, azeliragon, A-study) $\neq$ μ(ADAS-cog, P, A-study),

where μ(ADAS-cog, azeliragon, A-study) and μ(ADAS-cog, P, A-study) denote the true mean changes from Baseline at Month 18 on the ADAS-cog total score for the A-study azeliragon 5 mg/day added to SoC and placebo added to SoC groups, respectively.

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

- H_{02}: μ(CDR-sb, azeliragon, A-study)$=$ μ(CDR-sb, P, A-study)
- H_{12}: μ(CDR-sb, azeliragon, A-study) $\neq$ μ(CDR-sb, P, A-study).

where μ(CDR-sb, azeliragon, A-study) and μ(CDR-sb, P, A-study) denote the true mean changes from Baseline at Month 18 on the CDR-sb score for the A-study AD azeliragon 5 mg/day and placebo groups, respectively.

Hypothesis tests for B-study are as follows:

The first set of hypotheses to be tested in B-study (the third set of hypotheses for the study as a whole) is as follows:

- H_{03}: $\mu^{(\text{ADAS-cog, azeliragon, B-study})} = \mu^{(\text{ADAS-cog, P, B-study})}$
- H_{13}: $\mu^{(\text{ADAS-cog, azeliragon, B-study})} \neq \mu^{(\text{ADAS-cog, P, B-study})}$,

where $\mu^{(\text{ADAS-cog, azeliragon, B-study})}$ and $\mu^{(\text{ADAS-cog, P, B-study})}$ denote the true mean changes from Baseline at Month 18 on the ADAS-cog total score for the B-study azeliragon 5 mg/day added to SoC and placebo added to SoC groups, respectively.

The second set of hypotheses to be tested in B-study (the fourth set of hypotheses for the study as a whole) is as follows:

- H_{04}: $\mu^{(\text{CDR-sb, azeliragon, B-study})} = \mu^{(\text{CDR-sb, P, B-study})}$
- H_{14}: $\mu^{(\text{CDR-sb, azeliragon, B-study})} \neq \mu^{(\text{CDR-sb, P, B-study})}$.

where $\mu^{(\text{CDR-sb, azeliragon, B-study})}$ and $\mu^{(\text{CDR-sb, P, B-study})}$ denote the true mean changes from Baseline at Month 18 on the CDR-sb score for the B-study AD azeliragon 5 mg/day and placebo groups, respectively.

STAGE 2:

If and only if both hypothesis tests in A-study AD subjects and also B-study AD subjects for both co-primary variables (ADAS-cog and CDR-sb) have $p<0.05$, (i.e., $p<0.05$ for ADAS- cog demonstrating statistical superiority of azeliragon 5 mg added to SoC versus placebo added to SoC and also $p<0.05$ for CDR-sb demonstrating statistical superiority of azeliragon 5 mg added to SoC versus placebo added to SoC, i.e., statistical significance of the test of the null hypothesis for each A-study and B-study independently), testing will proceed to the fifth set of

hypotheses to the expansion of the more heterogeneous population of AD subjects participating in the study, including all study subjects.

Consistent with the FDA draft Guidance for Industry: *Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease* (February, 2012), toward the goal of demonstrating disease modification, analysis of MRI data (selection and specification will be made prior to database lock) will be done conditional on significance of the above named hypothesis tests:

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

- H_{05}: $\mu^{(MRI, azeliragon, All)} = \mu^{(MRI, P, All)}$
- H_{15}: $\mu^{(MRI, azeliragon, All)} \neq \mu^{(MRI, P, All)}$,

where $\mu^{(MRI, azeliragon, Alld)}$ and $\mu^{(MRI, P, All)}$ denote the true mean changes from Baseline at Month 18 on MRI volume measures for all AD azeliragon 5 mg/day and placebo groups, respectively.

It is noted that the specific MRI volume measures and specific statistical methodology for the MRI measures will be detailed in the SAP in accordance with a discussion with the FDA regarding the evolving scientific knowledge about the best correlates of changes in AD with MRI measures.

9.3 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 who are not treatment failures and who receive at least 6 months of study drug and attend at least 6 scheduled visits, 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 PPS also includes subjects who are treatment failures at any time during the study.

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). For purposes of this study, a subject is a completer if the subject has received treatment for 18 months and has efficacy data for 18 months.

The FAS will be used for all hypothesis tests of efficacy. Analysis of superiority using the PPS will also be done for supportive analyses.

The SAF will be used for safety analyses.

9.4 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 (disease history, medical history, and prior treatments for AD) will be summarized for all randomized patients and for the FAS.

A summary will also be provided for baseline-severity categories (ADAS-cog 19 or less; ADAS-cog more than 19). No formal statistical comparisons will be performed.

9.5 EFFICACY ANALYSIS

Efficacy evaluation will include the co-primary endpoints (ADAS-cog and CDR-sb), key secondary measures, and other efficacy markers.

A treatment failure is a subject who withdraws from the study due to lack of efficacy or due to toxicity, as assessed by a treatment-emergent adverse event that is judged associated with study medication. For purposes of efficacy analysis, a treatment failure is considered to have rendered final endpoint data. The latest on-treatment assessment is taken as the (hard) endpoint assessment. Taking the exit value as an endpoint value for a subject who is withdrawn from the study due to lack of efficacy is scientifically-based in a progressive disease where it is known that subjects due not spontaneously remit.

Statistical analysis will be done on each A-study and B-study, independently, for the co- primary variables: change from baseline in ADAS-cog and change from baseline in CDR-sb. sub-study, where A-study includes the first approximately 400 patients randomized and B-study includes the remaining approximately 400 patients randomized. For all other secondary variables, tertiary variables, and subgroup analyses, the study as a whole will be used for inferential purposes. It is noted that randomization supports independent analysis of A-Study and B-Study and also supports the statistical analysis of all randomized subjects.

9.5.1 Efficacy Variables of Analysis

9.5.1.1 Primary Efficacy Variables of Analysis

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

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

Key supportive variables will include mean change from Baseline to Visit in ADAS-cog and mean change from Baseline to Visit in CDR-sb.

9.5.1.2 Key Secondary Variables of Analysis

The key secondary endpoint will be one of the following (to be determined before breaking the blind for study treatment):

- Change from Baseline in hippocampal volume at Month 18.
- Change from Baseline in whole brain volume at Month 18.
- Change from Baseline in ventricular volume at Month 18.

9.5.1.3 Other Efficacy Variables of Analysis

Additional efficacy variables of analysis are as follows:

- Responder analysis at Months 1, 3, 6, 9, 12, 15 and 18 based on ADAS-cog and responder analysis at Months 3, 6, 12, and 18 based on the CDR-sb.
- The slope of the change over time in ADAS-cog, Mini-Mental State Examination (MMSE), and ADCS-ADL scales through Month 18.
- Time to loss of one global stage on the Clinical Dementia Rating (CDR) score through Month 18.
- Proportion of participants in each CDR global stage at Months 3, 6, 12 and 18.
- Change from Baseline on the ADAS-cog at Months 1, 3, 6, 9, 12 and 15 and at Months 3, 6 and 12 for the CDR-sb.
- Individual item responses on the Resource Utilization in Dementia Lite (RUD Lite) questionnaire and the total caregiver/informant time spent assisting the patient based on the RUD Lite at Months 5, 13 and 19.
- Proportion of participants who enter intermediate or long-term residential care (RUD Lite) at Months 6, 12, and 18.

- Change from Baseline in the Dementia Quality of Life (DEMQOL) -Proxy total score at Months 6, 12, and 18.

- Change from Baseline in the Neuropsychiatric Inventory (NPI) total score at Months 3, 6, 12, and 18.

- Change from Baseline on the Mini-mental State Examination (MMSE) total score at Months 3, 6, 12, and 18.

- Change from Baseline on the Continuous Oral Word Association Task (COWAT) score at Months 3, 6, 12, and 18.

- Change from Baseline on the Category Fluency Test (CFT) score at Months 3, 6, 12, and 18.

- Change from Baseline on the Trail Making Test (Versions A and B) time at Months 3, 6, 12 and 18

- Change from Baseline in the extent of brain glucose hypometabolism at Month 18.

- Change from Baseline in the severity of brain glucose hypometabolism at Month 18.

9.5.2 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, baseline stratum as a covariate, and subject as a random effect. Supportive modeling will also include MMRM main-effects model with treatment, time, and subject.

The primary analysis will be done for each sub-study separately and 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 primary analysis will also be done on randomization stratification subgroups defined by (1) baseline ADAS-cog 19 or less and (2) baseline ADAS-cog more than 19.

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 plus SoC than in the group treated with placebo plus SoC), a completers analysis (observed cases at Month 18), and 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-cog (CDR-sb) using last-observation-carried-forward (LOCF) methods for missing data, justified based on known profiles of ADAS-cog (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 plus SoC. For MMRM and ANCOVA, two-sided p-values will be displayed for the comparison against placebo plus SoC.

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.

Methodologies for analysis of MRI and FDG-PET data will be described in the SAP, possibly updated in accordance with published findings about relationships between changes in MRI and/or FDG-PET data and AD.

9.5.3 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, controlling for Stratum, if appropriate. 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-cog total score, will be assessed using cumulative percentage plots. Similarly, responders based on the CDR-sb score will be assessed using cumulative percentage plots. The y-axis will show the cumulative percentage of patients who achieved the specific measure of improvement in the ADAS-cog (or CDR-sb) total score shown on the x-axis with a separate cumulative percentage curve for each treatment group.

Time to loss of one global stage on the global CDR will include Kaplan-Meier curves. Survival estimates for treatment groups will be compared using the logrank statistic. Observations will be treated as right censored for participants who complete the study without a loss of one stage on the global CDR score or who discontinue the study prematurely.

The proportion of participants who experience loss of one global stage on the CDR will be assessed at each Visit using logistic regression with treatment (as a categorical/class variable), Baseline CDR global score (as a continuous variable).

Summary measures from the analysis will include the odds ratio, 95% confidence interval for the odds ratio, and p-value for treatment comparison. Additionally, the proportion of participants in each CDR global stage will be presented.

For change from Baseline in plasma concentrations of Aβ species, an MMRM analysis similar to that described for the co-primary endpoints with baseline plasma concentrations of Aβ species as a continuous covariate will be performed.

For change from Baseline in NPI and MMSE, an MMRM analysis similar to that described for the co-primary endpoints with baseline NPI, and MMSE, as a continuous covariate, respectively, will be performed.

Individual item responses on the RUD Lite questionnaire and the total caregiver/informant time spent assisting the patient based on the RUD Lite questionnaire will be summarized by treatment group.

For change from baseline in DEMQOL-Proxy total score, an ANCOVA analysis with Baseline DEMQOL-Proxy as a continuous covariate will be performed.

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 utilized.

9.5.4 Subgroup Analyses

Subgroup analyses will be based on the study as a whole. Subgroup analysis will include examination of consistency of efficacy results (ADAS-cog and CDR-sb) over subsets determined by demographic and baseline characteristics. The SAP will include details for subgroup analysis.

9.5.5 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.

9.6 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.

9.6.1 Safety Variables of Analysis

9.6.1.1 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

9.6.1.2 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 clinically significant abnormal values or changes in vital signs measures.

- Proportions of subjects with AEs related to vital signs

9.6.1.3 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) clinically significant values (Clinical laboratory-related AEs)or changes in laboratory values

9.6.1.4 Electrocardiography

Electrocardiography variables of analyses will include:

- Proportion of subjects with Corrections to QT intervals will be made by Bazett's method and also 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).

9.6.2 Statistical Methodology for Safety Analysis

Adverse events will be coded using MedDRA Version 16.0 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.

The following assessments are constructed to provide a view of safety assessments after more than one dose of study medication with variable exposure including assessments of change to worst value (to examine worse value, minimum and maximum values are examined):

- Baseline
- First on treatment
- Last on treatment
- Last available (includes off-treatment values and safety follow-up assessment values)
- Minimum value
- Maximum value

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

9.7 BRAIN MRI

Brain MRI data will be collected and analyzed for changes over the 18 month treatment period for safety or efficacy. The statistical methods will be described in the SAP.

9.8 PHARMACODYNAMIC DATA

All participants with at least one dose of study medication will be included in the pharmacokinetic and pharmacokinetic/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.

9.9 PHARMACOKINETIC DATA

Data resulting from blood sampling for trough concentrations of azeliragon will be collected and analyzed for changes over the 18 month treatment period. Concentration-driven analysis will be planned. The statistical methods will be described in the SAP.

A population pharmacokinetic analysis will be conducted to derive a model relating pre-dose steady state concentrations measured at each Visit, to estimates of individual clearance. The relevance of a range of covariates (e.g., age, weight) on model parameters will be evaluated.

Plasma concentrations will be determined to support concentration response analyses for selected plasma biomarkers, efficacy and safety data. Concentration-response plots will be derived and simple models fitted to the data to explore potential relationships. PK/PD models using either a Bayesian or maximum likelihood approach may be utilized to characterize these relationships and estimate pharmacokinetic and pharmacodynamic parameters.

9.10 DEMQOL AND OTHER QUESTIONNAIRES

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.

9.11 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.

A treatment failure is a subject who withdraws from the study due to lack of efficacy or due to toxicity, as assessed by a treatment-emergent adverse event that is judged associated with study medication (restated for convenience from Section 9.5 "Efficacy Analysis"). For purposes of efficacy analysis, a treatment failure is considered to have rendered final endpoint data. The latest on-treatment assessment is taken as the (hard) endpoint assessment. Any method of imputation will not alter this assessment.

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.

9.12 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 charter will guide operational aspects of the IDMC structure, processes, and study stopping rules.

9.13 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 this study.

As a conservative measure, an alpha adjustment is applied to accommodate up to 10 analyses by the IDMC. Alpha = 0.0001 is apportioned to each of no more than 10 analyses by the IDMC.

With the 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.

9.14 DATA MANAGEMENT CONSIDERATIONS

This study will utilize electronic data capture (EDC) for data capture. The database lock will occur for each sub-study (A-Study and B-Study) when the study is declared closed, when all subjects have completed the study (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 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. The database will house both A-Study and B-Study in a single database, but with the delineation of patients who are in A-Study and those who are in B-Study. The databases for each substudy will be locked separately (hard-lock). 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 sub-study as it completes. The database lock will occur for each sub-study (A-Study and B-Study) 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, signed by 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 Therapetuics 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 initiated 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 (1996).

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.

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

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

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.

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