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TITLE PAGE

CLINICAL TRIAL PROTOCOL

OPEN LABEL EXTENSION STUDY FOR CONTINUED SAFETY AND EFFICACY EVALUATION OF AZELIRAGON IN PATIENTS WITH MILD ALZHEIMER'S DISEASE

Investigational Product:	**TTP488**
Investigational Product Name:	**Azeliragon**
US IND Number:	**68,445**
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EudraCT Number:	**2016-002005-19**
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Clinical Phase:	**Phase 3**
Version and Date:	**AMENDMENT 1** **9AUGUST2017**

SIGNATURE CONFIRMATION PAGE

Investigational Product: **Azeliragon** (TTP488)

Study Number: TTP488-303

Protocol Title: **OPEN LABEL EXTENSION STUDY FOR CONTINUED SAFETY AND EFFICACY EVALUATION OF AZELIRAGON IN PATIENTS WITH MILD ALZHEIMER'S DISEASE**

Protocol Dated: **AMENDMENT 1 dated 9AUGUST2017**

I have reviewed and approved of the protocol listed above.

Dr. Larry Altstiel, M.D., Ph.D. 10 Aug 2017

Executive Vice President, Chief Medical Officer
vTv Therapeutics LLC

Signature Date

Imogene Dunn, Ph.D. 10 AUG 2017

Senior Vice President, Biometrics and Regulatory Affairs
vTv Therapeutics LLC

Signature Date

Aaron Burstein, Pharm.D. 10 Aug 2017

Senior Vice President, Clinical Development
vTv Therapeutics LLC

Signature Date

Document Revision History

Document	Version Date	Summary of Changes

Protocol Amendment 1	09 AUG 2017	• Section 4.2 Exclusion Criteria
		  ○ 3. Clarified that "change" from the TTP488-301 Baseline value intended to be an "increase".
		• Section 4.3. Added male contraceptive advice for fertile, sexually active males.
		• Section 5.5. Removed CYP3A4 inhibitors from list of prohibited conmeds.
		• Section 6.1 and Section 7.1.1 and Table 1. Revised to allow for vitals to be collected in a supine or sitting position.
		• Section 8.4. Clarified that adverse event assessment of relationship to study drug falls into one of two categories: related / not related.
		• Appendix 1. Modified Prohibited Medication List to remove CYP3A4 inhibitors.
		• Editorial Changes:
		  ○ Addition of reference in Section 1.1.1

Original re-issue	12 Oct 2016	• Editorial changes:
		  ○ Corrected page headers to remove "draft".
		  ○ Added Trail Making Test (TMT) abbreviation
		  ○ Added Reference 6.

Original Protocol	23 June 2016	N/A

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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 in patients with mild-to-moderate AD and even greater magnitude of benefit in patients with mild (MMSE 21-26) AD (ADAS-cog Δ=4.0, p<0.018; CDR-sb Δ=1.0, p=0.02). Thus, azeliragon has the potential to provide effective treatment of AD.

Objectives:

The primary objective of this study is:

- To collect long-term safety and tolerability data.

The secondary objectives of this study are:

- 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 measures of behavior, cognition, function, resource utilization, and quality of life.

Endpoints:

Primary Endpoints:

- Adverse events, clinical safety laboratory tests, ECG, vital signs.

Secondary Endpoints:

- The slope of change over time in ADAS-cog, CDR-sb, MMSE, ADCS-ADL, and NPI scales.
- Change from Baseline in measures of behavior, cognition, and function.

Study Design:

This is an open-label extension study in patients with mild Alzheimer's disease who have completed participation in the azeliragon Phase 3 (STEADFAST) trial. Patients will receive azeliragon 5 mg/day for up to 2 years.

SCHEDULE OF ACTIVITIES

Table 1. Schedule of Activities

Protocol Activity	Baseline	Treatment								Early Term
	Month 18 of TTP488-301 study	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	
Study Days		90	180	270	360	450	540	630	720	
Window		±14d	±14d	±14d	±14d	±14d	±14d	±14d	±14d	
Sign informed consent / provide assent	X*									
Registration	X*									
Review Inclusion/Exclusion Criteria	X*									
Body weight	X		X		X		X		X	X
Brief Neuro & Physical Exams	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Blood Pressure and Pulse Rate (sitting or supine)	X	X	X	X	X	X	X	X	X	X
12 Lead ECG	X		X		X		X		X	X
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing / Accountability	X*	X	X	X	X	X	X	X	X	X
Study Drug Dosing	X*	→	→	→	→	→	→	→		
MMSE	X		X		X		X		X	X
ADAS-cog	X	X	X	X	X		X		X	X
CDR	X		X		X		X		X	X
NPI	X		X		X		X		X	X
ADCS-ADL	X		X		X		X		X	X
COWAT	X		X		X		X		X	X
CFT	X		X		X		X		X	X
TMT	X		X		X		X		X	X
Columbia Suicide Severity Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X
RUD-lite	X		X		X		X		X	X
DEMQOL-proxy	X		X		X		X		X	X
Hematology	X		X		X		X		X	X
Blood Chemistry (incl HbA1c)	X		X		X		X		X	X
Pharmacokinetic Blood Sampling	X		X		X		X		X	X
Pharmacodynamic blood sampling (Aβ)	X		X		X		X		X	X

*procedures unique to OLE. All other baseline procedures are required TTP488-301 Month 18 procedures and are not repeated as part of the TTP488-303 baseline visit.

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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
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
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DEMQOL	Health-Related Quality of Life for People with Dementia
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th ed Text Revision
ECG	Electrocardiogram
FAS	Full analysis set
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

LIST OF ABBREVIATIONS (continued)

LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Methylmalonic Acid
MMSE	Mini-Mental State Exam
NASH	Nonalcoholic Steatohepatitis
NPI	Neuropsychiatric Inventory Questionnaire
PD	Pharmacodynamic
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
TMT	Trail Making Test
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 Open Label Extension study is designed to collect long term safety and tolerability data of azeliragon (TTP488) in participants with mild Alzheimer's disease (AD) who successfully completed the TTP488-301 study.

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, 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 triple by the year 2050 (Alzheimer's Association. 2016).

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.

Additionally, RAGE is believed to be involved in mediating advanced glycation endproduct induced tau hyperphosphorylation (Li et al., 2012). In vivo, injection of advanced glycation endproducts induced tau hyperphosphorylation, memory deterioration, decline of synaptic proteins and impairment of long-term potentiation. These effects are attenuated following blockade of the RAGE receptor with a RAGE antibody.

These data taken together suggest that inhibition of RAGE with an orally available small molecule inhibitor presents an attractive therapeutic rationale for the treatment of Alzheimer's disease.

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). There were no deleterious findings observed for either the 5-mg/day dose group or the placebo group. 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. Participants receiving 5 mg/day or placebo were re-consented and permitted to continue the study without modification.

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 (predicting a negative outcome) 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 TTP488-301 Phase 3 study is enrolling 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.

Patients who successfully complete the TTP488-301 study will be eligible to screen for this open label extension study.

1.1.4 Dose Selection Rationale

The azeliragon dose (5 mg daily) for the registration studies (TTP488-301) 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.

The relative bioavailability of a 5 mg dose of TTP488 administered as a single oral capsule under fed conditions (standard FDA high-fat breakfast) compared to the same formulation under fasted conditions in healthy volunteers was evaluated in Study TTP488-105. There was an approximately 20% reduction in exposure (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}72}$) following administration of a single 5 mg dose of TTP488 following a standard FDA high fat breakfast compared to dosing in the fasted state. Fed subjects experienced a greater lag time for absorption as compared to fasted subjects (median T_{lag} of 4 hours versus 1 hour post-dosing, respectively); however, the median T_{max} was the same between treatment groups (16 hours post-dosing). Geometric mean exposure estimates (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}72}$) were approximately 20% lower for subjects in the fed treatment group as compared to the fasted group. The results of the statistical analysis for bioequivalence in the presence or absence of food were consistent with a reduction of azeliragon exposure in the fed state for all parameters evaluated (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}72}$). The geometric least-squares mean ratio point estimates were approximately 80% for all PK parameters evaluated, with 90% confidence intervals that extended below the standard bioequivalence range (80% to 125%).

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

The primary objective of this study is:

- To collect long-term safety and tolerability data.

The secondary objectives of this study are:

- 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 measures of behavior, cognition, function, resource utilization, and quality of life.

2.2 ENDPOINTS

Primary Endpoints:

- Adverse events, clinical safety laboratory tests, ECG, vital signs.

Secondary Endpoints:

- The slope of change over time in ADAS-cog, CDR-sb, MMSE, ADCS-ADL, and NPI scales.
- Change from Baseline in measures of behavior, cognition, and function.

3.0 STUDY DESIGN

This is an open-label extension study in patients with mild Alzheimer's disease who have successfully completed participation in the azeliragon Phase 3 TTP488-301 (STEADFAST) trial. Patients will receive azeliragon 5 mg/day for up to 2 years.

Participants are required to continue to be on SoC of a stable background acetylcholinesterase inhibitor therapy and / or memantine 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.

Behavioral medications (including antidepressants, antipsychotics and anxiolytics) must be on stable doses. 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.

Subjects will participate in approximately 9 outpatient visits including baseline which is the same visit at the Month 18 visit in the TTP488-301 study.

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

- Principal Investigator (PI) – This person is responsible for the clinical evaluation of all participants, ensuring enrollment and protocol adherence, and endpoint determinations. 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.
- Non-CDR Rater – This person will meet the educational, clinical and scale experience requirements set by the sponsor. This person can conduct all ratings and assessments except the CDR ratings.
- 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. 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. Successful completion of Study TTP488-301 through the Month 18 Visit without ongoing SAEs or history of serious adverse drug reactions during study TTP488-301.

2. Patients must enroll in the present study within 7 days of completion of study TTP488-301.

3. 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.

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

5. The subject must have a reliable caregiver/informant with regular contact (i.e., 10 hours a week as a combination of face-to-face visits and telephone contacts are 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.

6. 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.

7. 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. The subject is felt by the investigator to be unsuitable (on the basis of health, compliance, caregiver availability, or for any other reason) for inclusion in the study.

2. Subjects with serious suicide risk. If there are "yes" answers on items 4, 5 or on any behavioral question of the C-SSRS, a suicide risk assessment must 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.

3. Subjects demonstrating a QTcF > 480 msec or a >45 msec increase from the TTP488-301 Baseline value based on the locally read ECG performed at the TTP488-301 Month 18 Visit (TTP488-303 Baseline). Participants with known history of bundle branch block (either right or left) are allowed if absolute QTcF value does not exceed 500 msec. Participants with a functioning pacemaker, indicated by an ECG displaying paced rhythm, are allowed with no QTc upper limit.

4. 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 2-year 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(s) 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

TTP488-303 is not a randomized study. All eligible subjects will receive azeliragon 5 mg / day.

5.2 BREAKING THE BLIND

TTP488-303 is an open label study.

5.3 DRUG SUPPLIES

Drug supplies will consist of a 5 mg azeliragon supplied as a Size 2 hard gelatin capsule. The recommended storage condition for the product is room temperature at 15ºC to 30ºC (59ºF to 86ºF).

5.3.1 Formulation and Packaging

Azeliragon will be packaged into child-resistant, high density polyethylene (HDPE) bottles with heat induction seal (HIS) closures.

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 following confirmation of eligibility. One capsule will be administered with a glass of water. Participants will be instructed to take one capsule per day by mouth for the duration of the treatment period. The day's dose of azeliragon will be administered in the clinic at each subsequent study visit. Azeliragon may be administered without regard to meals.

5.3.3 Compliance

Participants will bring all unused azeliragon 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. Any change in dose or frequency must be captured in the eCRF.

All Medications taken after the first dose of study medication in the open label extension 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) 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:

- Considerations for use of medications that may affect the CNS or cognition following enrollment in the open label extension. When 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). Should their use be deemed to be chronic (spanning months), discussion with the Sponsor's medical monitor is required.

The use of following concomitant medications is not allowed:

- Drugs known to be potent CYP2C8 or any other prohibited concomitant drugs (See APPENDIX 1

  PROHIBITED MEDICATION LIST for a partial 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 other investigational therapies for Alzheimer's disease that are being investigated for possible disease modification activity (e.g., passive immunotherapies and secretase inhibitors) or non-disease modifying purposes are allowed during this study.

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 proximal 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.

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

- ECGs: obtain prior to blood sampling.

- 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.

6.1 STUDY PERIOD

6.1.1 Baseline (Month 18 of TTP488-301)

Following completion of the TTP488-301 Month 18 Visit procedures, 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).

After obtaining consent, the following baseline activities will be completed.

- Review of inclusion and exclusion criteria
- If eligible, registration for the TTP488-303 study
- Dispense study drug if eligible.
- Subject begins taking study medication in the clinic as soon as baseline procedures are completed.

The TTP488-301 Month 18 assessments will also serve as the Baseline assessments for the TTP488-303 Open Label Extension. The visit procedures that are unique to the TTP488-303 baseline visit can be completed up to 7 days following the Month 18 visit for the TTP488-301 study. The 7 day window will begin on the TTP488-301 Month 18 visit day. To participate in TTP488-303, the subject must be registered and study drug is administered within 7 days of the TTP488-301 Month 18 visit day.

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 to ensure that the patient continues to be appropriate for the study.

6.1.2 Month 3 (± 14 days)

- ADAS-cog.
- 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.
- Vital signs: blood pressure and pulse rate.
- 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.

6.1.3 Month 6 (± 14 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 and pulse rate.
- Blood 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.

6.1.4 Month 9 (± 14 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.
- Vital signs: blood pressure and pulse rate.
- 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.

6.1.5 Month 12 (± 14 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 and pulse rate.
- Blood 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.

6.1.6 Month 15 (± 14 days)

- 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.
- Vital signs: blood pressure and pulse rate.
- 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.

6.1.7 Month 18 (± 14 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 and pulse rate.
- Blood 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.

6.1.8 Month 21 (± 14 days)

- 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.
- Vital signs: blood pressure and pulse rate.
- 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.

6.1.9 Month 24 (± 14 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 and pulse rate.
- Blood sampling for safety laboratory testing including HbA1c.
- Collect blood samples for PK and PD.
- Drug accountability. Any discrepancies are recorded in the source.
- End of study procedures

6.2 EARLY TERMINATION

In the event a subject discontinues participation prior to completion of the Month 24 visit the following procedures should be performed.

- ADAS-cog, MMSE, CDR, ADCS-ADL, COWAT, CFT, Trail Making Tests (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 and pulse rate.
- Blood sampling for safety laboratory testing including HbA1c.
- Collect blood samples for PK and PD.
- Drug accountability. Any discrepancies are recorded in the source.

6.3 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 a final visit, if applicable, 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 based on a specific adverse event profile as recommended by the Sponsor in discussions with the PI. 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, 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 in a sitting or supine position. Vital signs will be conducted in the same position (sitting or supine) at all the study visits and position captured in the source documentation. Participants should be sitting or 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. Each original recording will be evaluated by the PI or designee following the measurement. The interpretation of results will follow the categories "normal," "abnormal, NCS," or "abnormal, CS". An abnormal measurement may be repeated at the PI or designee discretion. If the abnormal ECG measurements are considered as clinical significant, the abnormality will be recorded as AE in the eCRF.

When assessing eligibility at the Baseline 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 4. 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. 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's TTP488-301 Month 18 ECG will be reviewed locally in order to verify continued eligibility for the study. If the QTcF is >480 msec based on the local QTcF reading, the participant is not eligible. If the QTcF represents an increase from TTP488-301 Baseline of > 45 msec, the participant is not eligible.

At any time during the study, a subject with an absolute QT > 480 msec or an increase from baseline in QTcF > 45 msec should prompt a call to the Sponsor's medical monitor for guidance on how to proceed.

7.1.3 Physical Examination

Brief physical examination will include skin, eyes, oral mucosa, cardiac, and respiratory. A brief physical examination will be conducted at all study visits. Body weight will be also examined at the Baseline (Month 18 of TTP488-301), Month 6, Month 12, Month 18, and Month 24 study visits.

7.1.4 Neurological Examination

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 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 Baseline (Month 18 of TTP488-301), Months 6, 12, 18, and 24 or at time of premature discontinuation. All routine laboratory tests will be analyzed by a central laboratory, which will provide instructions and supplies.

Hematology	Chemistry
Hemoglobin	BUN and Creatinine
Hematocrit RBC count	Glucose
Platelet count WBC count	Calcium
MCV	Sodium
Total neutrophils (Abs)	Potassium
Eosinophils (Abs)	Chloride
Monocytes (Abs)	Total CO2 (Bicarbonate)
Basophils (Abs)	AST
Lymphocytes (Abs)	ALT
	GGT
	LDH
	Total Bilirubin
	Alkaline phosphatase
	Uric acid
	Albumin
	Total protein
	HbA1c

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 CDR may be done on a separate proximal visit day to avoid patient fatigue. 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

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

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 Baseline (Month 18 of TTP488-301) and at Months 3, 6, 9, 12, 18, and 24 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 Baseline (Month 18 of TTP488-301), and at Months 6, 12, 18, and 24 or in the event of early termination. Scores range from 0-30 with lower scores indicating greater cognitive impairment.

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 (Month 18 of TTP488-301), and at Months 6, 12, 18, and 24 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 (Month 18 of TTP488-301), and at Months 6, 12, 18, and 24 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 (Month 18 of TTP488-301), and at Months 6, 12, 18, and 24 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 (Month 18 of TTP488-301), and at Months 6, 12, 18, and 24 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 Baseline (Month 18 of TTP488-301) and at Months 6, 12, 18, and 24 or in the event of early termination. CDR may be done on a separate proximal visit day to avoid patient fatigue.

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 Baseline (Month 18 of TTP488-301), and at Months 6, 12, 18, and 24 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 (Month 18 of TTP488-301) and at Months 6, 12, 18, and 24 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 (Month 18 of TTP488-301) and at Months 6, 12, 18, and 24 or in the event of early termination.

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.

The C-SSRS will be used to assess suicide ideation or behavior at each study 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 at Baseline (Month 18 of TTP488-301), Months 6, 12, 18 and 24 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.

Following blood collection, the tubes will be placed in an ice-water bath (maximum 60 minutes) until centrifugation. 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 (Month 18 of TTP488-301), Months 6, 12, 18, and 24 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 BLOOD VOLUME

Total blood sampling volume for the individual participants is approximately 106 mL.

Sample Type	Sample Volume (mL)	Number of Sampling Times	Total Volume (mL)
Routine Laboratory	16.5	4	66
PK	4	4	16
Biomarkers (Aβ)	6	4	24
TOTAL (mL)			106

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 24. 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: A direct cause and effect relationship exists, or is likely to exist, between the AE and the study drug in the judgment of the investigator. (i.e., there is evidence or arguments to conclude that the study drug caused the adverse event)

- Not Related: The AE is not related to the study drug, if in the judgment of the investigator, 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 of *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, in consultation with the 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 database lock for the study. The SAP will supersede the protocol. Any deviations from the planned analyses will be described in the final integrated study report.

This open-label, single-arm study includes subjects who completed TTP488-301, in which they were randomized to receive azeliragon (plus SoC) or placebo (plus SoC). An analysis plan for the meta-analysis combining data from TTP488-301 with this study will be done prior to database lock for this study. It is intended that the key analysis of results from this open-label study be described in the integrated analysis plan, and that the analysis of this study alone be described in this protocol.

SAS Version 9.4 or later will be used. Medical dictionary for Regulatory Activities (MedDRA) Version 18.0 or later will be used for coding adverse events. Medications will be coded using WHO Drug Dictionary (WHODD) Version March 2009 or later.

Continuous data will be summarized using descriptive statistics (number, mean, median, standard deviation, first and third quartiles, minimum, and maximum). Categorical data will be summarized for the enrolled population and also by treatment group according to the randomization of TTP488-301 using frequency tables (frequencies and percents).

Baseline will be the latest available data point prior to the first dose of study medication in this study (start of treatment for this protocol).

Outliers that are detected during the review of the data will be investigated. Methods for dealing with outliers will be defined in the SAP. In general, missing data will not be imputed, and outliers will not be excluded unless they are considered to be erroneous values.

9.1 POPULATIONS OF ANALYSIS

Populations of analysis are defined as follows:

- The full analysis set (FAS) includes all enrolled patients with on-treatment data. The FAS is used for all efficacy analyses.
- The per-protocol set (PPS) includes all FAS patients who are not excluded due to a significant protocol violation, where a significant protocol violation is one that has the potential to affect analysis conclusions. Final determinations of significant protocol violations will be made at the final blind data review meeting in accordance with guidance from ICH E9 (Statistical Principles).
- The safety set (SAF) includes all patients who received at least one dose of study medication. The SAF is used for all safety analyses.

To understand the impact of subjects who withdraw from the study prior to completion, the FAS will be partitioned into groups of subjects who complete the study (completers) and subjects who do not complete the study (dropouts).

9.2 DISPOSITION, DEMOGRAPHIC, AND BASELINE DATA

A tabulation of subject disposition will be presented, including the number enrolled for the single group of enrolled population, the number enrolled by treatment group according to the randomized treatment from Study TTP488-301, the number dosed in each population group, the number who withdrew prior to completing each part of the study, and reasons for withdrawal.

Demographic and baseline characteristics (disease history, medical history, and prior treatments) will be summarized for all randomized patients and for the FAS. No formal statistical comparisons will be performed.

9.3 SAFETY ANALYSIS

A treatment-emergent adverse event (TEAE) is defined as an AE that was not present at baseline, or an exacerbation of a pre-existing AE. For laboratory data, a treatment-emergent abnormal laboratory value (TEAV) represents an abnormal value that was normal at baseline.

Safety variables of analysis include the following:

- Proportions of patients with any TEAEs
- Proportions of patients with serious TEAEs
- Proportions of patients with severe TEAE
- Proportions of patients with TEAEs leading to study drug discontinuation
- Proportions of patients with TEAEs leading to study withdrawal
- Proportions of patients with drug-related TEAEs
- Proportions of patients with TEAVs
- Proportions of patients meeting DILI criteria
- Proportions of patients meeting ICH E14 criteria for threshold values or threshold changes
- Mean changes from baseline in vital signs
- Mean changes from baseline in clinical laboratory measures
- Mean change from baseline in measures from electrocardiography

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, median, standard deviation, first and third quartiles, minimum, and maximum). Categorical data will be summarized by treatment group using frequency tables (frequencies and percentages).

9.4 EFFICACY ANALYSIS

Efficacy variables will include changes from baseline in scores from questionnaire data and cognition and performance assessments. Time to threshold changes will be defined in the SAP for the integrated analysis of the data from this study with the data from TTP488-301.

Continuous data will be summarized by treatment group using descriptive statistics (number, mean, median, standard deviation, first and third quartiles, minimum, and maximum). Categorical data will be summarized by treatment group using frequency tables (frequencies and percentages).

Baseline will be the latest available data point prior to start of treatment.

Outliers that are detected during the review of the data will be investigated. Methods for dealing with outliers will be defined in the SAP. In general, missing data will not be imputed, and outliers will not be excluded unless they are considered to be erroneous values. Sensitivity analyses and exploratory analyses may be done using imputation or excluding outliers to ensure robustness of study conclusions.

9.5 HANDLING MISSING DATA

In general, no imputation of values for missing data will be performed, except as otherwise described for efficacy evaluation. Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

Sensitivity analyses will be done to assess the impact of missing data or spurious data on study conclusions. Sensitivity analyses will include methods of imputation, which will be defined in the SAP. Methods of imputation may include favorable imputation (regardless of treatment), unfavorable imputation (regardless of treatment), last-observation-carried-forward, and worse-observation-carried-forward; baseline values will not be carried forward.

9.6 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.

Based on the review of safety data, the IDMC will make recommendations regarding the conduct of the study. These may include amending safety-monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed.

The IDMC charter will specify these and other operational aspects of the IDMC structure, processes and study stopping rules.

9.7 INTERIM ANALYSIS

No interim analysis is planned for this study.

9.8 DATA MANAGEMENT CONSIDERATIONS

This study will utilize electronic data capture (EDC) for data capture. The database lock will occur 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 based on a risk based approach 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)". The database lock will occur when the study is declared closed, when all participants have completed the study (last visit of the last subject on-study) and the data are fully monitored with all queries resolved.

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

Any missing or inconsistent data entries will be referred back to the PI or designee, using a data query form, and documented for each individual study participant before eCRFs are frozen, 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 Therapeutics needs to be notified and approval obtained before records may be transferred off site.

12.0 ETHICS

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

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

A protocol amendment may be 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 (2013).

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

12.3 SUBJECT INFORMATION AND CONSENT

Informed consent will be administered in accordance with the requirements of 21 CFR 50.20-27, FDR C.05.010 and ICH E6 4.8, Principles of Good Clinical Practice, as applicable. Before protocol-specified procedures are carried out, the PI and study staff will explain the objectives of the study, study procedures, as well as the risks involved to the study participant, his/her legally authorized representative (if applicable) and caregiver/informant prior to their inclusion in the trial.

Prior to performing any study-specific procedure, each study participant and the participant's caregiver/informant will be required to read and voluntarily sign an Institutional Review Board (IRB)/Research Ethics Board (REB)- approved informed consent form (ICF), indicating his/her consent to participate (or assent in the case of participants who are deemed to be unable to have the cognitive ability to provide consent [where this is in accordance with local laws, regulations and ethics committee policy]). 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

1. Alzheimer's Association. 2016 Alzheimer's Disease Facts and Figures. Alzheimer's & Dementia 2016;12(4).

2. Arancio O, Zhang HP, Chen X, Lin C, Trinchese F, Puzzo D, et al. RAGE potentiates Abeta- induced perturbation of neuronal function in transgenic mice. EMBO J. 2004 Oct;23(20):4096-105.

3. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. Prog Cardiovasc Dis 2001;43(5 Suppl 1):1-45.

4. Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull. 1988;24:637-9.

5. Bierhaus A, Humpert PM, Morcos M, Wendt T, Chavakis T, Arnold B, et al. Understanding RAGE, the receptor for advanced glycation end products. J Mol Med. 2005 Nov;83(11):876-86.

6. Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. Neuropsychologia 1967;5:135-40.

7. Carrano A, Hoozemans JJM, Van der Vies SM, Rozemuller AJM, Van Horssen J, De Vries HE. Amyloid Beta induces oxidative stress-mediated blood-brain barrier changes in capillary amyloid angiopathy. Antioxid Redox Signal. 2011 Sep;15(5):1167-78.

8. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308-14.

9. Deane R, Du Yan S, Submamaryan RK, LaRue B, Jovanovic S, et al. RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. Nat Med. 2003 Jul;9(7):907-13.

10. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "http://medicine.iupui.edu/clinpharm/ddis/clinical- table/" Accessed 5August2013.

11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of participants for the clinician. Journal of Psychiatric Research 1975;12:189-98.

12. Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997;11 Suppl 2: S33-9.

13. Guidance for Industry. Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendation. DRAFT GUIDANCE. February 2012.

14. Hartz AMS, Bauer B, Soldner ELB, Wolf A, Boy S, Backhaus R, et al. Amyloid-β contributes to blood-brain barrier leakage in transgenic human amyloid precursor protein mice and in humans with cerebral amyloid angiopathy. Stroke. 2012 Feb;43(2):514-23.

15. Kook S-Y, Hong HS, Moon M, Ha CM, Chang S, Mook-Jung I. $A\beta_{1-42}$-RAGE interaction disrupts tight junctions of the blood-brain barrier via Ca^{2+}-calcineurin signaling. J Neurosci. 2012 Jun;32(26):8845-54.

16. Li XH, Lv BL, Xie JZ, Liu J, Zhou XW, Wang JZ. AGEs induce Alzheimer-like tau pathology and memory deficit via RAGE-mediated GSK-3 activation. Neurobiol Aging. 2012 Jul;33(7):1400-10.

17. Loonstra AS, Tarlow AR, Sellers AH. COWAT metanorms across age, education, and gender. Appl Neuropsychol 2001;8:161-6.

18. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimers Dement. 2011;7(3):263-9.

19. Posner, K., et al., The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168: 1266-77.

20. Reitan R. Validity of the trail making test as an indicator of organic brain disease. Perceptual and Psychomotor Skills 1958;8:271-6.

21. Rocken C, Kientsch-Engel R, Mansfeld S, et al. Advanced glycation end products and receptor for advanced glycation end products in AA amyloidosis. Am J Pathol. 2003;162:1213-20.

22. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. American Journal of Psychiatry 1984;141:1356-64.

23. Schmidt AM, Sahagan B, Nelson RB, Selmer J, Rothlein R, Bell JM. The role of RAGE in amyloid-beta peptide-mediated pathology in Alzheimer's disease. Curr Opin Investig Drugs. 2009 Jul;10(7):672-80.

24. Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. Health Technol Assess. 2005;9(10):1-93.,iii-iv

25. Stern D, Yan SD, Yan SF, Schmidt AM. Receptor for advanced glycation endproducts: a multiligand receptor magnifying cell stress in diverse pathologic settings. Adv Drug Deliv Rev. 2002;54(12):1615-25.

26. Tanzi RE, Moir RD, Wagner SL. Clearance of Alzheimer's Abeta peptide: the many roads to perdition. Neuron. 2004;43:605-8.

27. Wimo A, Gustavsson A, Johnsson L, Winblad B, Hsu MA, Gannon B. Application of a resource utilization in dementia (RUD) instrument in global setting. Alzheimers Dement. 2012; epub

28. Yan SD, Chen X, Fu J, Chen M, Zhu H, Roher A, Slattery T, Zhao L, Nagashima M, Morser J, Migheli A, Nawroth P, Stern D, Schmidt AM. RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. Nature 1996 Aug;382(6593):685–691.

29. Yan SD, Zhu H, Zhu A, et al. Receptor-dependent cell stress and amyloid accumulation in systemic amyloidosis. Nat Med. 2000;6:643-51.

30. Yan SD, Chen X, Walker DG, Schmidt AM, Arancio O, Lue LF. RAGE: a potential target for Abeta-mediated cellular perturbation in Alzheimer's disease. Curr Mol Med. 2007;7(8):735-42.

31. Yan SD, Bierhaus A, Nawroth PP, Stern DM. RAGE and Alzheimer's disease: a progression factor for amyloid-beta-induced cellular perturbation? J Alzheimers Dis. 2009;16(4):833-43.

APPENDICES

APPENDIX 1

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
monteleukast
pioglitazone

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "http://medicine.iupui.edu/clinpharm/ddis/clinical-table/" Accessed 5Aug2013.

Guidance for Industry. Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendation. *DRAFT GUIDANCE*. February 2012.