PROTOCOL TITLE: A Phase 2 Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of BHV-4157 in Patients With Mild to Moderate Alzheimer's Disease

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CLINICAL STUDY PROTOCOL

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Protocol Number: BHV4157-203

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STUDY SUMMARY

Title	A Phase 2 Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of BHV-4157 in Patients with Mild to Moderate Alzheimer's Disease
Rationale	BHV-4157 is a new chemical entity 3rd-generation prodrug of the glutamate modulator, riluzole, which has been designed to bypass first-pass metabolism therein providing greater bioavailability, diminished PK variability, lower hepatic burden, lack of food effect, longer half-life and once daily dosing. Preclinical models suggest that riluzole, the active metabolite of BHV-4157, may protect from AD-related pathology and cognitive dysfunction.
Target Population	Male and females, age 50 to 85 years (inclusive at screening), diagnosed with Alzheimer's Disease (in accordance with NIA/Alzheimer's Association Guidelines) of mild to moderate severity including MMSE score 14-24 at the screening visit. Eligible participants should be receiving a stable dose of FDA-approved AD medication(s) (acetylcholinesterase inhibitors (AchEI) and/or memantine) for at least 3 months prior to screening and willing to remain on same dose(s) for trial duration. Those participants with contraindications or failed treatment with either AchEI and/or memantine will be eligible for inclusion.
Number of Participants	Approximately 336 participants will be randomly allocated using a 1:1 allocation to active treatment or placebo.
Drug Dosage & Treatment Duration	Titrated dose of BHV-4157 to 280 mg, or placebo, taken orally once daily. Duration of double-blind treatment is approximately 48 weeks. There is also a screening period of up to 42 days; and a 4-week post-treatment observation period. Eligible subjects will have the opportunity to continue in a 48-week open-label extension phase (once it is open for recruitment at their investigative site).
Objectives	**Randomized Double-Blind Treatment Phase** **The co-primary objectives are to:** evaluate the efficacy of BHV-4157 as measured by a) ADAS-Cog 11, and b) CDR-Sum of Boxes. **The secondary objectives are to:** (1) evaluate the efficacy of BHV-4157 as measured by: volumetric MRI (Quarc bilateral hippocampal volume)

	Neuropsychiatric Inventory (NPI), ADCS-ADL, and Mini-Mental State Examination (MMSE). (2) evaluate the safety and tolerability of BHV-4157 as measured by mortality rates, serious adverse events, adverse events, clinical safety laboratories, physical examinations and significant ECG changes. **Exploratory objectives are to assess**: (1) Efficacy of BHV-4157 assessed by the Montreal Cognitive Assessment (MoCA); (2) efficacy of BHV-4157 on performance using the AD Composite Score (ADCOMS); (3) volumetric MRI (bilateral lateral ventricles and whole brain volume); (4) efficacy of BHV-4157 on performance on a cognitive composite outcome computed using measures from the NACC Neuropsychological Test Battery; (5) pharmacokinetics of BHV-4157 and riluzole in plasma; (6) treatment response by Apo E genotype; and (7) CSF, serum and plasma biomarkers (Aß42, Aß42/40 ratio, total tau, p-tau-181, neurogranin, NfL, YKL-40, VILIP, SNAP-25, sTREM2, GFAP) at screening, week 24 and week 48 of the double-blind phase. CSF will be assessed in a subset of the study population (estimated n=50 active, n=50 placebo). **Exploratory Open-Label Extension (OLE) Phase objective is to** evaluate the safety and tolerability of BHV-4157 as measured by mortality rates, serious adverse events, adverse events, clinical safety laboratories, physical examinations and significant ECG changes. Additional exploratory objective of evaluating long-term effects on clinical outcome measures.
Study Design & Statistical Plan	This is a phase 2 multi-center, randomized, double blind, placebo-controlled, parallel group study followed by an optional 48 week Open-Label Extension phase. Stratification factors will be site and MMSE score at screening (moderate AD: 14 to 19; mild AD: 20 to 24). The co-primary endpoints are mean within-participant change in ADAS-Cog 11 and CDR Sum of Boxes from baseline to week 48 of the double-blind phase, compared between the treatment and placebo arms. The primary objective of the trial is met if both co-primary endpoints are significantly in favor of treatment at the 5% level. CCI [redacted]

	CCI  **Overall study power at the final analysis of the 48 week double-blind phase:** The study has at least 80% power to detect a difference between the BHV-4157 arm and the placebo arm in mean 12 month change of 2.64 points on the ADAS-Cog 11 and of 0.95 points in CDR Sum of Boxes, under a range of interim effect sizes which give 93.7% probability of proceeding at the interim analysis. **Statistical methods:** Both the interim and final analysis of the 48 week double-blind phase will use a mixed effects repeated measures model. The co-primary endpoints at the final analysis are both required to attain 5% significance level in order to be reported. If both co-primary outcomes are significant, then the remainder of the secondary outcomes will be tested at overall 5% significance level using a Holm step-down test. This will preserve alpha at 5% overall for all endpoints reported. The primary analysis for the study will take place after all subjects have completed all visits in the double-blind phase.
Co-Primary Endpoints	The mean change in ADAS-Cog 11 from baseline to week 48 of the double-blind phase, compared between the BHV-4157 treatment group and the placebo group. The mean change in CDR-Sum of Boxes from baseline to week 48 of the double-blind phase, compared between the BHV-4157 treatment group and the placebo group.

Secondary Endpoints	The change in the NPI total score from baseline to week 48 of the double-blind phase. The change in ADCS-ADL total score from baseline to week 48 of the double-blind phase. The change in MMSE from baseline to week 48 of the double-blind phase. The change in MRI Quarc bilateral hippocampal volume from screening to week 48 of the double-blind phase. The change in safety and tolerability measures including: (1) adverse events; (2) clinical laboratory tests; (3) vital signs; (4) physical examinations; (5) ECGs.
Exploratory Endpoints	Exploratory endpoints include: (1) the change in MoCA scores from baseline to week 48 of the double-blind phase; (2) the change in ADCOMS total score from baseline to week 48 of the double-blind phase; (3) the change in MRI Quarc bilateral lateral ventricles and whole brain volume from screening to week 48 of the double-blind phase; (4) the change in composite z score from baseline to week 48 of the double-blind phase on the cognitive composite outcome computed using measures from the NACC Neuropsychological Test Battery; (5) BHV-4157 and riluzole pharmacokinetics; (6) treatment response in participants by Apo E genotype; and (7) CSF, serum and plasma biomarker panel (Aß42, Aß42/40 ratio, total tau, p-tau-181, neurogranin, NfL, YKL-40, VILIP, SNAP-25, sTREM2, GFAP) will be assessed at screening, week 24, and week 48. CSF will be assessed in a subset of the study population (estimated n=50 active, n=50 placebo).
Interim Analysis Endpoints	The mean change in ADAS-Cog 11 from baseline to week 24 of the double-blind phase, compared between the BHV-4157 treatment group and the placebo group. The mean change in MRI Quarc hippocampal volume from screening to week 24 of the double-blind phase, compared between the BHV-4157 treatment group and the placebo group.

Exploratory Open-Label Extension Endpoint	The safety and tolerability measures in the Open-Label Extension include rates of: (1) adverse events; serious adverse events, suspected unexpected serious adverse reactions (2) clinically abnormal laboratory tests; (3) shifts in vital signs; (4) physical examination abnormalities; (5) ECG abnormalities. Additional exploratory endpoint of evaluating long-term effects on clinical outcome measures.

PROTOCOL SUMMARY OF CHANGES

Number	Brief description summary of changes	Date
Version 01 –Original Draft	Not Applicable	26 April 2018
Version 02	Administrative updates, refinement of inclusion/exclusion criteria, addition of concomitant medication considerations.	14 Jun 2018
Version 03	Modification of Primary and Secondary Objectives and Endpoints, to include a Co-Primary Endpoint. Increase in sample size. SAP update to match change in endpoints. Clarification of CCI [redacted] plans. Unscheduled visit added to protocol. Administrative clarifications/updates.	01 Oct 2019
Version 04	Added additional window for Week 48 visit in order to proactively account for any subjects that may potentially be out of visit window due to concerns related to COVID-19 pandemic. Allowing remote safety visits if needed due to COVID-19.	16-MAR-2020
Version 05	Added Open-Label Extension Phase and made minor edits to the COVID-19 language	24-Apr-2020
Version 06	Moved the volumetric MRI (Quarc bilateral lateral ventricles and whole brain volume)and neuropsychological test battery from secondary to exploratory outcome. Clarification of mITT population.	10-SEP-2020

STUDY SCHEMATIC

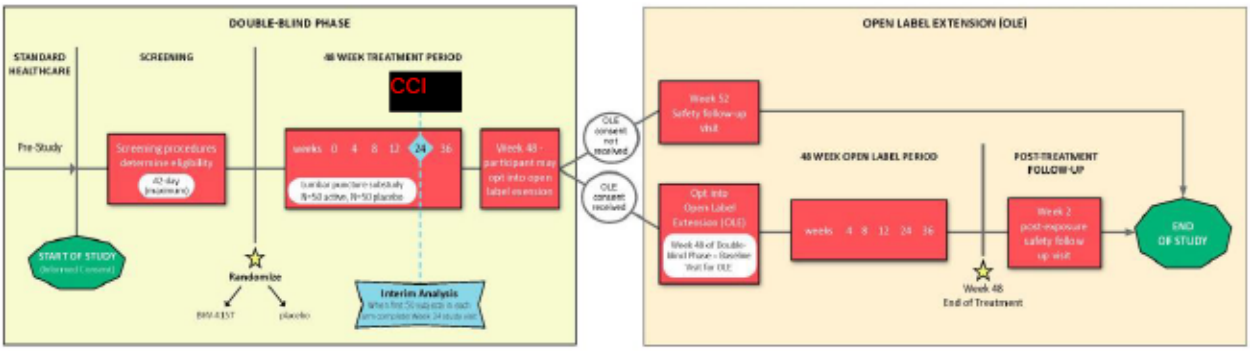


TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Aβ	β-Amyloid
AchEI	Acetylcholinesterase Inhibitor
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive (subscale)
ADCOMS	Alzheimer's Disease Composite Score
ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory
ADME	Absorption, Distribution, Metabolism, Excretion
AICD	Automatic Implanted Cardioverter Defibrillator
AUC	Area Under the Curve
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine Aminotransferase
ApoE	Apolipoprotein E
AST	Aspartate Aminotransferase
BDNF	Brain-derived Neurotrophic Factor
BID	Twice per day
BUN	Blood Urea Nitrogen
CDR-SOB	Clinical Dementia Rating- Sum of Boxes
CFR	Code of Federal Regulations
CJD	Creutzfeldt-Jakob Disease
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatinine Phosphokinase
CSF	Cerebrospinal Fluid
CYP	Cytochrome P450
DMP	Data Management Plan
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data Safety & Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food & Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HIPAA	Health Insurance Portability & Accountability Act
hr (unit)	Hour
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent-To-Treat
kg (unit)	Kilogram
LAR	Legally Authorized Representative

LBD	Lewy Bodies Dementia
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LFT	Liver Function Test
LP	Lumbar Puncture
MAD	Multiple Ascending Dose
MCI	Multiple Cerebral Infarctions
MINT	Multi-lingual Naming Test
mITT	Modified Intent-To-Treat
mg (unit)	Milligram
ml (unit)	Milliliter
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NfL	Neurofilament Light (Protein)
ng (unit)	Nanogram
NIA	National Institute on Aging
NOAEL	No-observed-adverse-effect-level
NPH	Normal Pressure Hydrocephalus
NPI	Neuropsychiatric Inventory
OHRP	Office of Human Research Protection
PHI	Personal Health Information
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PSP	Progressive Supranuclear Palsy
QD	Once per day
Quarc	Quantitative Anatomical Regional Change
RBC	Red Blood Cell
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCA	Spinocerebellar Ataxia
SD	Standard Deviation
SSC	Study Steering Committee
sTREM2	Soluble Variant Triggering Receptor Expressed on Myeloid Cells 2
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
USPI	United States Prescribing Information
VILIP	Visinin-Like Protein
vMRI	Volumetric Magnetic Resonance Imaging
WBC	White Blood Cell

1 INTRODUCTION

1.1 Background

More than 5 million people are afflicted with Alzheimer's disease (AD) in the United States, and by 2050 this number could rise as high as 16 million (Dementia, 2017). Recent data suggests that AD affects twice as many females as males, and is thought to be associated with multiple biological and genetic factors. The emotional and financial burden of AD to patients, family members, and society is enormous, and is predicted to grow exponentially as the median population age increases. The potential to preserve, or even improve, cognition in adults at high risk of cognitive decline due to AD clearly has important implications, not only for the affected individual, but also for the support system that bears the social and financial burdens of long-term caregiving.

There are medications currently approved for symptomatic treatment of AD, but they have small effect sizes and generally limited clinical benefits. An urgent need exists to find effective treatments for AD that can arrest or reverse the disease before its advanced stages. Therapeutic strategies aimed at restoring synaptic and extra synaptic glutamate levels, offer potential therapeutic benefit in AD, in cognition, as well as in the neuroprotection of synapses, conferring the potential for disease modification. The significance of clinical research directed at this preclinical validated synaptic target cannot be overstated, given the lack of therapeutic progress in symptomatic and disease-modifying treatments since 2003.

Biohaven Pharmaceuticals, Inc. [Biohaven] is developing a new drug, BHV-4157, for the potential treatment of mild to moderate Alzheimer's Disease as well as for other neurologic and psychiatric disorders. BHV-4157 is a novel and optimized prodrug of the glutamatergic agent riluzole. The FDA originally approved riluzole (RILUTEK®) 50 mg twice-a-day (NDA #20-599) for the treatment of patients with amyotrophic lateral sclerosis (ALS). Riluzole is only indicated for ALS and has a number of non-desirable attributes that have limited its clinical use. BHV-4157 is a tripeptide prodrug of the glutamate modulating agent riluzole that has been optimized for improved bioavailability, pharmacokinetics and dosing.

More specifically, BHV-4157 was developed to address the limitations of riluzole that have restricted its broader clinical application. Riluzole tablets have 60% bioavailability, attributed to high first-pass metabolism in the liver. This is thought to be related to metabolism by the heterogeneously expressed CYP1A2 enzyme, which also accounts for the high PK variability associated with riluzole (Carlsson, 2000; Pittenger, 2015a, 2015b). In addition, riluzole is associated with reduced exposure when taken with meals (i.e., a negative food effect), resulting in the guidance to take riluzole within a three hour fast (one hour before or two hours after a meal).

Riluzole is also dosed twice a day, has dose-dependent effects on liver function tests and the drug substance itself has other intrinsic limitations including: very low solubility in water, poor oral palatability, pH dependent chemical stability, and intense oral numbness if administered directly to the oral mucosa.

Based on the preclinical features of BHV-4157, we anticipate the clinical pharmacology to offer favorable properties as compared to available riluzole. These include:

- **Improved Bioavailability**—BHV-4157 is a substrate for the gut transporters (PepT1). This is thought to contribute to its increased bioavailability as compared to orally-dosed riluzole, meaning that more of the compound is absorbed by the body into the blood stream and can have an active effect. Studies have shown that administration of agents through peptide transporters significantly increases the absorption of drugs with otherwise poor oral bioavailability.

- **No Negative Food Effect**—BHV-4157 shows no food effect in human studies, meaning that the drug will not be associated with special meal restrictions, a phenomenon potentially attributable to enhanced uptake by intestinal transporters specific to the peptide-containing moiety of BHV-4157. This is in contrast to oral riluzole tablets, which require a 3-hour window of fasting around its two daily doses to reach therapeutic levels, currently a dose-limiting factor of riluzole.

- **Lower Overall Drug Burden to the Liver**— as a prodrug that mitigates first-pass liver metabolism and enhances bioavailability, therapeutic concentrations of the active metabolite riluzole can be achieved with a lower drug dose as compared to riluzole tablets. In addition, release of the active metabolite over time will result in a reduced bolus hepatic concentration as compared to that associated with riluzole tablets. Taken together, we believe these attributes of BHV-4157 will reduce the potential for adverse liver effects.

- **Optimized Dosing Regimen and Compliance**—BHV-4157 has been developed as a convenient once daily dose, which could improve regimen compliance for patients. We believe these are important features to optimize long-term health outcomes in the treatment of patients with chronic diseases.

1.2 Preclinical & Scientific Rationale

Synaptic loss is a fundamental and consistent pathobiological feature of AD. Indeed, synaptic loss in the hippocampus and neocortex provides the strongest anatomical correlations to disease severity (Terry et al., 1991). Furthermore, there is increasing evidence from post-mortem studies implicating glutamatergic synaptotoxicity in AD, resulting in decreased synaptic plasticity. In AD, there is reduced functional glutamate transporter concentration (excitatory amino acid transporter 2: EAAT2), with resultant elevated synaptic extracellular glutamate.

A neurotoxic cycle of increased extracellular glutamate activates NMDA receptors and leads to a reduction in downstream trophic effectors, including CREB and BDNF, causing cell death and atrophy (Hardingham, 2006). Increased extracellular glutamate also leads to increased amyloid-beta (Aβ) production (Bordji, Becerril-Ortega, Nicole, & Buisson, 2010), which can further increase glutamate release with reduced synaptic uptake (Chin et al., 2007; Matos, Augusto, Oliveira, & Agostinho, 2008; Scimemi et al., 2013) and increased tau release (Hunsberger et al., 2015). Decreases in EAAT2 correlate to synaptic loss and disease severity.

Animal model data including behavioral observations further support and extend these findings. In one experimental model, a double transgenic mouse (TG) with amyloid overproduction ($A\beta PP_{swe}$/PS1EΔ9) lacking one allele for the EAAT2 showed accelerated and increased cognitive

impairment compared to TG mice with both EAAT2 alleles (Mookherjee et al., 2011). In another study, a TG mouse approach crossing EAAT2 transgenic mice with $APP_{Sw,Ind}$ mice and a pharmacological approach using an EAAT2 translational activator were conducted. Findings from both approaches demonstrated that restored EAAT2 protein function improved pathology, while the $APP_{Sw,Ind}$ using an EAAT2 translational activator approach also improved clinical phenotype and pathology (Takahashi et al., 2015). Thus, there is model support for EAAT2 as a therapeutic target to impact glutamatergic synaptic NMDA interactions.

Glutamate transporter 1 (GLT-1), the mouse homologue of the EAAT2, expresses predominately on astrocytes and is responsible for regulating 90% of glutamate levels in the synapses. In a study by Zumkehr et al. using a triple transgenic mouse model of AD (3xTg-AD), GLT-1 was pharmacologically overexpressed by administering ceftriaxone, and results showed that the chronic upregulation of GLT-1 significantly attenuated tau pathology, restored synaptic proteins, and rescued cognition without affecting Aβ pathology (Zumkehr et al., 2015). Specifically, on a behavioral basis, ceftriaxone-treated mice had better memory performance (Morris Water Maze and Novel Object Recognition). In this paradigm, the GLT-1 dysfunction and improvement did not appear to be related to amyloid species or pathology. This behavioral finding was further supported on a molecular basis via ELISA and histological analyses showing that GLT-1 dysfunction did not affect amyloid precursor protein (APP) processing, overall Aβ species levels, or plaque pathology in 3xTg-AD mice. Of further interest was the histopathological finding that ceftriaxone-treated 3xTg-AD mice had significantly less CP13-positive tau (pSer202) bearing neurons in the cortex and hippocampus. Similarly, the mean intensity from immunofluorescence staining with the PHF-1 antibody (pSer396/Ser404) was significantly less than the vehicle group in the CA1 region of the hippocampus. Quantitative analysis of fluorescent signals revealed that synaptic proteins detected by SYP and PSD-95 antibodies were significantly preserved in the CA3 region of the hippocampus of ceftriaxone-treated 3xTg-AD mice. Furthermore, a significant restoration of PSD-95 immunoreactivity in the CA1 region of the hippocampus was also observed in ceftriaxone-treated 3xTg-AD mice. Restoration of PSD-95 also showed a correlation with augmented cognitive performance by the Morris Water Maze. Overall, these findings indicate that increasing GLT-1 may play a pivotal role in preserving synapses and neuron-to-neuron communication in AD.

In the P301L tauopathy mouse model, Hunsberger et al (2015) demonstrated that treatment with riluzole at 12 mg/kg/day improved memory performance and that improvement was associated with a decrease in glutamate release and an increase in glutamate uptake in the dentate gyrus region of the hippocampus. Riluzole treatment also reduced tau pathology and increased hippocampal GLT-1 and PSD-95 expression.

In aged rats, GLT-1 gene expression is significantly reduced and treatment with riluzole significantly increases GLT-1 gene expression and decreases hippocampal cytokine levels. This highlights the therapeutic potential of enhancing glutamate transport in diseases characterized by neuroinflammation and neurodegeneration (Brothers et al., 2013). RNA sequencing, validated by qRT-PCR open arrays, has been used to confirm increases in GLT-1 gene expression in response to riluzole treatment (Pereira et al., 2017). Another study, investigating the effects of riluzole on memory decline in aged rats (10-months old) treated with riluzole or vehicle for 17 weeks (Pereira et al., 2014), found that the aged riluzole-treated rats did not exhibit age-related cognitive decline

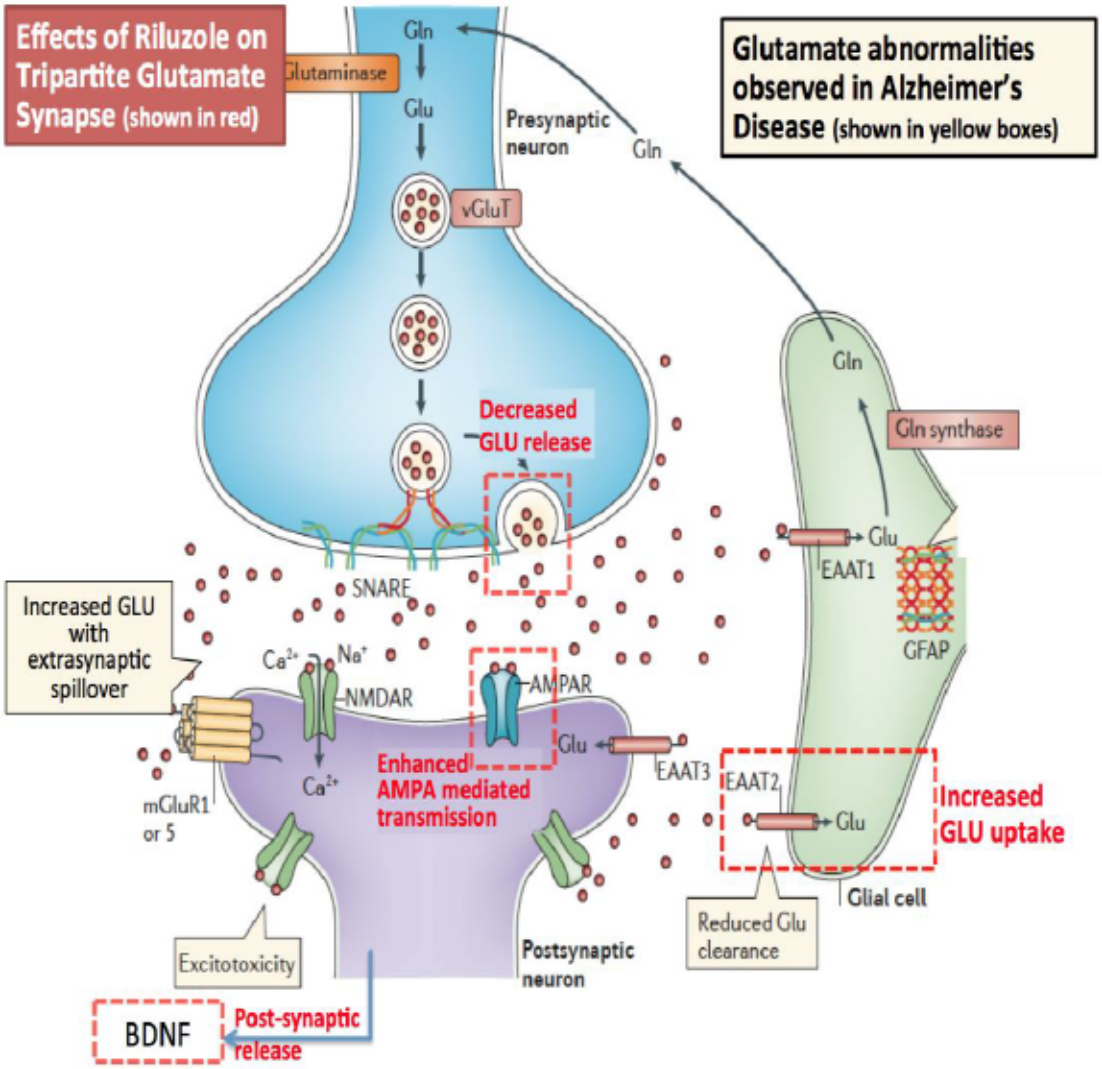
over time in the Y-maze test (a hippocampal-dependent task) compared with aged-control rats. Moreover, memory performance was correlated with the density of thin spines on apical dendrites in the CA1 region of the hippocampus. Riluzole-treated rats had an increase in clustering of thin spines that correlated with memory performance and was specific to the apical, but not basilar, dendrites of CA1. Other studies investigating the effect of riluzole on glutamate uptake in rat astrocyte cultures have showed a biphasic concentration-dependent effect on basal glutamate uptake with low concentrations (1 and 10 microM) of riluzole significantly increasing glutamate uptake (Frizzo, Dall'Onder, Dalcin, & Souza, 2004).

Neuronal hyper excitation occurs in transgenic mouse models overexpressing APP and its pathogenic product, Aβ protein. The cellular basis of this has been pursued in rat models using brain tissue slices with bath application of soluble $A\beta_{1-42}$ and with riluzole treatment to investigate whether a persistent sodium current (I_{NaP}) may, in part, account for the Aβ-induced neuronal hyperexcitation (Ren et al., 2014). Results showed that soluble $A\beta_{1-42}$ increased neuronal excitability in a concentration-dependent manner and increased the amplitude of I_{NaP} without significantly affecting its activation properties. In the presence of riluzole, the $A\beta_{1-42}$ induced neuronal hyperexcitation and I_{NaP} augmentation were significantly inhibited. These findings suggest that soluble $A\beta_{1-42}$ may induce neuronal hyperexcitation by increasing the amplitude of I_{NaP} and that riluzole can inhibit the $A\beta_{1-42}$-induced abnormal neuronal activity.

1.3 Mechanism of Action

The active metabolite of BHV-4157, riluzole, has been documented to have a wide range of pharmacological actions, including interactions with several types of ion channels, cellular signaling mechanisms, and facilitation of glutamate reuptake. The figure below illustrates the potential targets related to riluzole's mechanism of action: (1) Reducing presynaptic glutamate release through actions at the voltage-gated ion channels, (2) Facilitation of glutamate uptake via EAATs located on glial cells, (3) Enhanced transmission through synaptic AMPA receptors, (4) Altering GABAergic neurotransmission (5) Effects on neurotrophic agents such as BDNF. Several of these actions of riluzole balance abnormalities observed in human post-mortem tissue as well as in animal models. As such, BHV-4157 potentially offers neuroprotective effects at the level of the synapse as well as improved synaptic functioning, mechanisms that could exert both symptomatic and disease-modifying effects in AD.

Figure 1. Mechanism of Action (Riluzole)



1.4 CCI

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1.6 Potential for Drug-Drug Interactions

BHV-4157: BHV-4157, itself, is not expected to interfere with drug metabolism, and its cleavage via plasma peptidases renders it unlikely to be affected significantly by liver cytochrome P450 inhibitors. BHV-4157 has the following known pharmacokinetic/metabolism parameters:

- Not an inhibitor of CYP3A4, CYP1A2, or CYP2D6
- In CYP induction studies:
    - The estimated EC50 and E_{max} for CYP1A2 mRNA was 1.44 µM and 3.47-fold induction, respectively
    - The estimated EC50 and E_{max} for CYP2B6 mRNA was 12.6 µM and 27.0-fold induction, respectively
    - BHV-4157 did not increase CYP3A4 mRNA at doses up to 30 µM

Riluzole Metabolism: BHV-4157 metabolizes to riluzole. As per the USPI, riluzole metabolism has been assessed in special populations, characterized by hepatic impairment (2 to 3 fold increase in AUC with Child-Pugh Scores of A and B), renal impairment (no effect), age (no effect), sex (no effect), smokers (20% faster elimination) and race (Japanese compared to Caucasians: no effect).

Effect of other drugs on riluzole metabolism: In vitro studies using human liver microsomal preparations suggest that CYP1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole and, therefore, potential interactions may occur when riluzole is given concurrently with agents that affect CYP1A2 activity. Potential inhibitors of CYP1A2 (e.g., ciprofloxacin, enoxacin, fluvoxamine, methoxsalen, mexiletine, oral contraceptives, thiabendazole, vemurafenib, zileuton) could decrease the rate of riluzole elimination, while inducers of CYP1A2 (e.g., cigarette smoke, charcoal-broiled food, rifampicin, and omeprazole) could increase the rate of riluzole elimination.

Effect of riluzole on the metabolism of other drugs: CYP1A2 is the principal isoenzyme involved in the initial oxidative metabolism of riluzole; potential interactions may occur when riluzole is given concurrently with other agents which are also metabolized primarily by CYP1A2 (e.g., theophylline, caffeine, and tacrine). Currently, it is not known whether riluzole has any potential for enzyme induction in humans.

It is possible that BHV-4157 may reduce the efficacy of co-administered drugs that are sensitive substrates of CYP1A2 and CYP2B6.

1.7 Clinical Experience

To date, BHV-4157 has been well tolerated and no new tolerability or safety signals compared to the previously approved riluzole have been observed. Data from clinical studies of BHV-4157 are briefly summarized below. Please refer to the Investigator's Brochure for additional clinical information.

1.7.1 Adverse Event Profile

1.7.1.1 BHV-4157

CCI

Study BHV4157-201 was a double-blind, placebo-controlled study conducted with BHV-4157 to assess safety, tolerability and efficacy in participants with SCA, which is a progressive, genetic, degenerative neurological disease. Participants received BHV-4157 140 mg once daily or placebo for 8 weeks. A total of 141 participants were enrolled into the study. Overall, BHV-4157 140 mg once daily for 8 weeks was well tolerated in adult participants with SCA. The majority of adverse events were mild or moderate in severity. There were no deaths reported in this study. Treatment-emergent SAEs were reported for 5 (3.55%) participants, including 4 BHV-4157-treated participants (asthenia, atrial fibrillation, blood creatinine phosphokinase increased, dehydration, back pain and cerebral infarction), and 1 placebo-treated participant (chest discomfort). No SAE reported in the BHV-4157 group was judged by the investigator to be treatment related. The completion rate was 90.14% (64/71 participants) in the BHV-4157 group and 97.14% (68/70 participants) in the placebo group. The frequency of treatment-emergent AEs that led to withdrawal from study drug was 4.23% (3/71 participants) in the BHV-4157 group and no participant in the placebo group. The majority of treatment-emergent AEs during the Double-Blind Randomization phase (Safety Analysis Set) were mild or moderate in severity, not related to study therapy, and resolved spontaneously by the end of treatment. The most frequently (≥ 5%) reported treatment-emergent AEs were:

Treatment-emergent AE	Number of Participants (%)	Study Group
Dizziness	8 (11.27%) 1 (1.43%)	BHV-4157 Placebo
Fatigue	6 (8.45%) 3 (4.29%)	BHV-4157 Placebo
Fall	5 (7.04%) 1 (1.43%)	BHV-4157 Placebo
Headache	4 (5.63%) 4 (5.71%)	BHV-4157 Placebo
Nausea	4 (5.63%) 4 (5.71%)	BHV-4157 Placebo
Muscle Spasms	4 (5.63%) 2 (2.86%)	BHV-4157 Placebo

No clinically meaningful trends in laboratory values were identified in this study. No participant had AST or ALT laboratory abnormalities > 3 X ULN. Participants completing the double-blind treatment phase were offered 48 weeks of open-label treatment with BHV-4157 (140 mg PO QD) in an Open-Label Extension phase. One hundred and thirty-one (131) participants continued into the Open-Label Extension phase. The safety profile of BHV-4157 140 mg QD during long-term treatment (randomization and extension phases through the 07-Sep-2018 data cutoff date) was consistent with the BHV-4157 safety profile observed during the double blind treatment phase.

1.7.1.2 Riluzole

Clinical information on riluzole, as reflected in the USPI, is predominantly based on experience from approximately 4000 patients given riluzole for ALS. Refer to the USPI where greater details on the adverse event profile of riluzole can be found. The following summarizes relevant information.

Overall, riluzole tablets have been well tolerated in populations with ALS and diverse neuropsychiatric conditions that include major depressive disorder, generalized anxiety disorder and spinocerebellar ataxia. In randomized controlled trials comparing a 100 mg daily dose of riluzole with placebo, no AEs occurred at rates greater than 5% and twice that of placebo. The AEs occurring greater than 5% and at least 2% more than placebo included asthenia (18% vs 12% placebo) and nausea (14% vs 9%). These two AEs showed trends for a dose response (Lacomblez, Bensimon, Leigh, Guillet, & Meininger, 1996). The published literature on the use of riluzole tablets in psychiatric disorders, while generally comprised of case-series, is consistent with this tolerability profile.

The most commonly observed AEs associated with the use of riluzole tablets more frequently than placebo treated patients were:

- asthenia
- nausea
- dizziness
- decreased lung function
- diarrhea
- abdominal pain
- pneumonia
- vomiting
- vertigo
- circumoral paresthesia
- anorexia
- somnolence

Approximately 14% (n = 141) of the 982 individuals with ALS who received riluzole in pre-marketing clinical trials discontinued treatment because of an adverse experience. Of those patients who discontinued due to adverse events, the most commonly reported were: nausea, abdominal pain, constipation, and ALT elevations. In a dose response study in ALS patients, the rates of discontinuation of RILUTEK® for asthenia, nausea, abdominal pain, and ALT elevation were dose

related. The AEs of asthenia, nausea, dizziness, diarrhea, anorexia, vertigo, somnolence, and circumoral paresthesia were dose related. Assessment of pulmonary AEs is confounded by the underlying illness, ALS, which is associated with respiratory symptoms.

1.7.1.3 Elevations in Liver Function Tests

BHV-4157 has not been associated with significant changes in liver function or pathology in nonclinical toxicology studies to date, as reflected in the Investigator's Brochure. No clinically significant LFT changes were observed on study drug in BHV4157-101. No participant had AST or ALT laboratory abnormalities > 3 X ULN in BHV4157-102, BHV4157-103 or BHV4157-201. BHV4157-203, BHV4157-206, and BHV4157-207 are blinded and ongoing. Preliminary safety findings are based on available randomized, double-blind data. As of 22-Jan-2020, 1 subject discontinued from BHV4157-207 and 1 subject discontinued from BHV4157-203 due to increased liver function tests.

Riluzole is associated with elevations in aminotransferases that have been reflected in monitoring precautions that will be followed within this protocol. Experience in almost 800 ALS patients indicates that about 50% of riluzole-treated patients will experience at least one ALT/SGPT level above the upper limit of normal, about 8% will have elevations > 3 X ULN, and about 2% of patients will have elevations > 5 X ULN. A single non-ALS patient with epilepsy treated with concomitant carbamazepine and phenobarbital experienced marked, rapid elevations of liver enzymes with jaundice (ALT 26 X ULN, AST 17 X ULN, and bilirubin 11 X ULN) four months after starting riluzole; these returned to normal 7 weeks after treatment discontinuation. Maximum increases in serum ALT usually occurred within 3 months after the start of riluzole therapy and were usually transient when < 5 X ULN. In trials, if ALT levels were < 5 X ULN, treatment continued and ALT levels usually returned to below 2 X ULN within 2 to 6 months. Treatment in studies was discontinued, however, if ALT levels exceeded 5 X ULN, so that there is no experience with continued treatment of ALS patients once ALT values exceed 5 X ULN. There were rare instances of jaundice. There is limited experience with rechallenge of patients who have had riluzole discontinued for ALT > 5 X ULN, but there is the possibility of increased ALT values reoccurring. Therefore, rechallenge is not recommended. In post-marketing experience, cases of clinical hepatitis associated with riluzole have been reported, including one with fatal outcome.

1.7.1.4 Neutropenia

BHV-4157 has not been associated with hematologic findings in nonclinical toxicology studies to date. In Study BHV4157-101, one participant in the 17.5 mg BID cohort experienced transient and mildly decreased white blood cell count after three days of treatment; however, this participant evidenced moderate decline during the screening period prior to medication administration. The participant's count increased while on continued study drug and normalized within 6 days after onset. No clinically meaningful trends in laboratory values were identified in Study BHV4157-201.

For riluzole, according to the USPI, rare cases of neutropenia were reported. Among approximately 4,000 patients given riluzole for ALS in clinical trials, there were three cases of marked neutropenia (absolute neutrophil count less than 500/mm3), all seen within the first 2

months of riluzole treatment. In one case, neutrophil counts rose on continued treatment. In a second case, counts rose after therapy was stopped. A third case was more complex, with marked anemia as well as neutropenia, and the etiology of both is uncertain. Patients should be warned to report any febrile illness to their physicians. The report of a febrile illness should prompt treating physicians to check white blood cell counts.

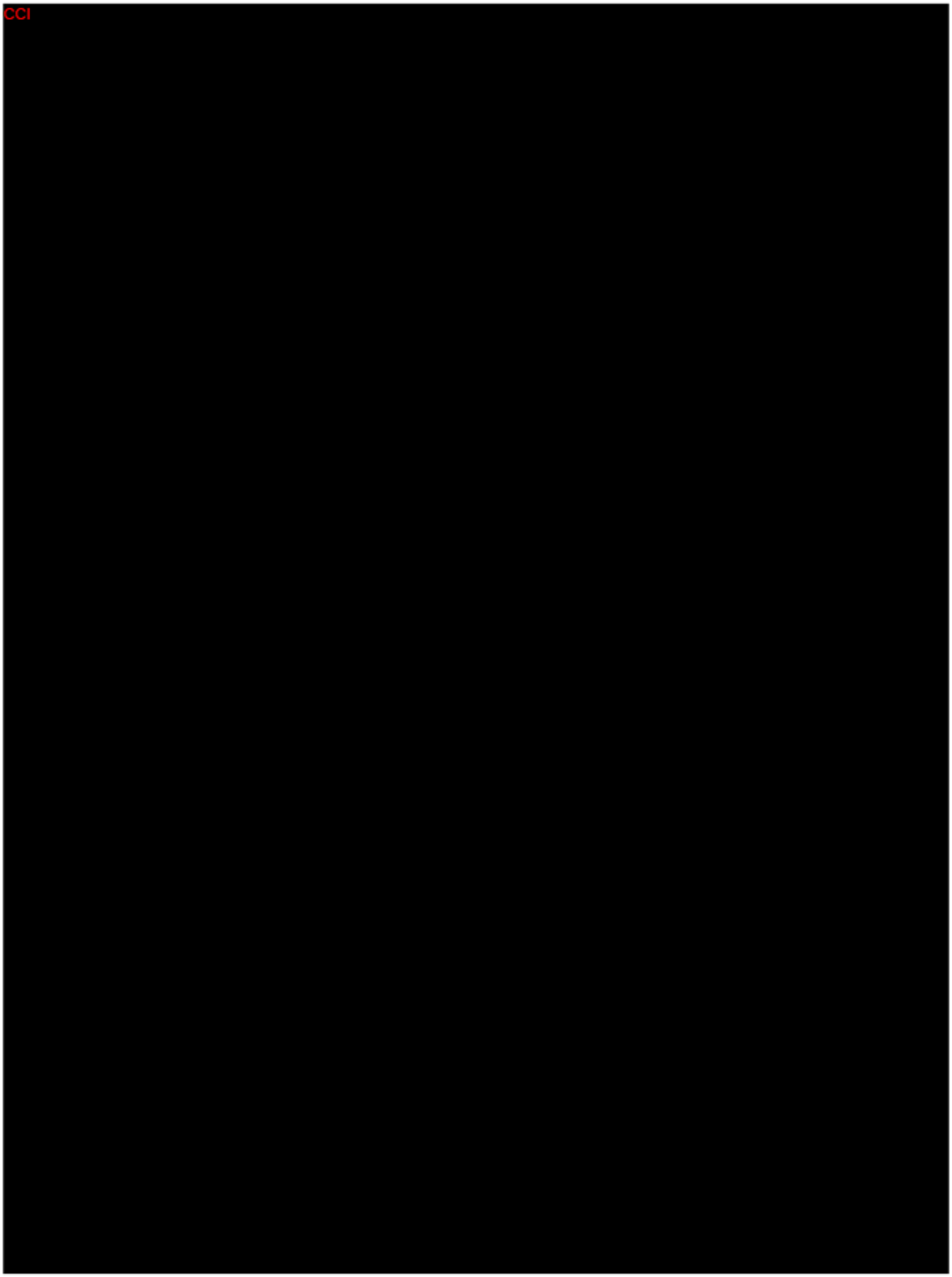
1.7.1.5 Interstitial Lung Disease

BHV-4157 has not been associated with pulmonary findings in nonclinical toxicology studies to date and no clinically significant pulmonary findings to date in clinical studies.

For riluzole, according to the USPI, rare cases of interstitial lung disease have been reported, some of them severe; upon further investigation, many of these cases were hypersensitivity pneumonitis. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease or hypersensitivity pneumonitis (e.g. bilateral diffuse lung opacities), riluzole should be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.

1.8 CCI

CCI



1.9 Potential Risk to Fetal Development

BHV-4157 has not yet been assessed in fertility and fetal development studies.

Riluzole has been assessed previously and has been characterized as a Category C drug. As described in the USPI, oral administration of riluzole to pregnant animals during the period of organogenesis caused embryo toxicity in rats and rabbits at doses of 27 mg/kg and 60 mg/kg, respectively, or 2.6 and 11.5 times, respectively, the recommended maximum human daily dose on a mg/m^2 basis. Evidence of maternal toxicity was also observed at these doses. When administered to rats prior to and during mating (males and females) and throughout gestation and lactation (females), riluzole produced adverse effects on pregnancy (decreased implantations, increased intrauterine death) and offspring viability and growth at an oral dose of 15 mg/kg or 1.5 times the maximum daily dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Riluzole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2 STUDY DESIGN

This is a phase 2 multi-center, randomized, double blind, placebo-controlled, parallel group study in patients with mild to moderate Alzheimer's disease.

Participants will be randomized to one of two groups: 280 mg of BHV-4157 or placebo. The BHV-4157 treatment dose of 280 mg was selected for evaluation in the current study based on evidence summarized in Section 1.8. Double-blind treatment duration is approximately 48 weeks (12 months). There is a screening period of up to 42 days and a 4-week post-treatment observation period (for subjects who do not participate in the Open-Label Extension phase).

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In addition, subjects who are completing or have completed the Double-blind treatment phase may be offered the opportunity to enroll in an Open-Label Extension phase, in which subjects will receive open-label treatment with BHV-4157 for approximately 48 weeks. Enrollment into the Open-Label Extension phase for all subjects is contingent on the PI's judgement that open-label treatment offers an acceptable risk-benefit profile for each individual. All subjects who enter the Open-Label Extension phase will need to sign a new informed consent form.

- Participants who are completing the double-blind treatment phase may directly enter the Open-Label Extension phase. These participants should not complete the follow-up safety visit at Week 52 (of the double-blind treatment phase). Instead, these participants should continue directly into the Open-Label Extension phase starting at Week 48 (of the double-blind treatment phase). The Week 48 visit will serve as the Baseline visit in the Open-Label Extension phase for participants who are going directly from the double-blind treatment phase to the OLE. Thereafter, participants will undergo visits at Week 4, Week 8, Week 12, and then every 12 weeks of the Open-Label Extension phase as outlined in Table 3 (Schedule of Assessments/Time & Events- Extension Phase).
- Participants who previously completed the double-blind treatment phase prior to the Open-Label Extension phase of the study being open for recruitment at their study center, may also enter the Open-Label Extension phase.
    - For participants who will have been off of the study drug for less than or equal to 4 weeks, the subject should come into the investigative site for an Abbreviated Drug Dispensation Visit (also "Abbreviated OLE Baseline Visit"), at which time any major medical or medications changes will be reviewed prior to dispensing riluzoleIn this case, most procedures from the Week 48 visit will also serve as the Open-Label Extension phase Baseline visit, as outlined in Table 3 (Schedule of Assessments/Time & Events- Extension Phase). Thereafter, participants will undergo visits at Week 4, Week 8, Week 12, and then every 12 weeks of the Extension Phase.

- For participants who have been off the study drug for greater than 4 weeks, these participants should be re-assessed and re-consented by the PI during an Open-Label Extension Baseline Visit. From the date that the Open-Label Extension is open for recruitment at the study site, these participants that completed the study prior will have up to approximately 12 weeks to complete the Open-Label Extension Baseline Visit. Thereafter, participants will undergo visits at Week 4, Week 8, Week 12, and then every 12 weeks of the Open-Label Extension phase as outlined in Table 3 (Schedule of Assessments/Time & Events- Extension Phase). All previous completers of the double-blind phase will have a 12-week window of opportunity to baseline into the OLE, regardless of their date of double-blind phase completion. In the event sites open for Open-Label recruitment, then close due to COVID-19 before enrolling all prior completers, exceptions to the 12-week window will be considered on a case-by-case basis following discussion with the Sponsor Medical Monitor:

Sponsor Medical Monitor

PPD PPD

Cell: PPD

PPD

- As with the double-blind phase, certain provisions may be implemented, in order to minimize potential hazards to study participants due to COVID-19. These provisions may allow alternatives to in-person study visits and include but are not limited to the following: conducting remote visits via phone/telemedicine video, focusing on safety assessments during remote visits, performing safety labs via local labs or professional in home phlebotomy vendors, and shipping study medication to study participants if needed. Any potential issues should be discussed with the Sponsor and will be addressed on an individualized basis.
- Participants who early-terminated from the double-blind phase trial or discontinued the study drug for any reason will not be eligible for enrollment in the Open-Label Extension phase.
- All participants must have their Week 48 visit in-person prior to enrolling in the Open-Label Extension phase. (Due to COVID-19, the timing of this visit may be delayed).

All subjects entering the Open-Label Extension phase will start with one capsule of BHV-4157 (140 mg) per day and titrate to two capsules per day after week two (280 mg). This will be done so that all participants will be on open-label medication and will safely continue from either active BHV-4157 or placebo.

All subjects in the Open-Label Extension phase are planned to undergo a termination visit two weeks after the last dose of study drug.

3 OBJECTIVES

3.1 Co-Primary Objectives

There are two co-primary objectives:

- Evaluate the efficacy of BHV-4157 as measured by ADAS-Cog 11
- Evaluate the efficacy of BHV-4157 as measured by CDR-Sum of Boxes

3.2 Secondary Objectives

The secondary objectives are to evaluate the efficacy, safety and tolerability of BHV-4157 as outlined below.

3.2.1 Efficacy

The efficacy of BHV-4157 will be assessed by the following measures:

- Volumetric MRI (Quarc bilateral hippocampal volume)
- Neuropsychiatric Inventory (NPI)
- Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)
- Mini-Mental State Examination (MMSE)

3.2.2 Safety and Tolerability

The safety and tolerability of BHV-4157 will be assessed by the following measures:

- Mortality rates
- Serious adverse event rates
- Adverse events
- Clinical safety laboratories
- Vital signs
- Physical examinations
- ECGs
- Use of concomitant medications

3.3 Exploratory Objectives

Exploratory objectives are to assess:

- Efficacy of BHV-4157 assessed by the Montreal Cognitive Assessment (MoCA)
- Evaluate the efficacy of BHV-4157 on performance using the AD Composite Score (ADCOMS)
- Volumetric MRI (bilateral lateral ventricles and whole brain volume)

- A cognitive composite outcome computed using measures from the NACC Neuropsychological Test Battery [Craft Story 21 Recall (Immediate & Delayed); Benson Complex Figure (Copy & Delayed Recall); Multilingual Naming Test; Letter & Category Fluency; Trail Making Test A & B; Number Span Forward and Backward]
- Pharmacokinetics of BHV-4157 and riluzole in plasma
- Treatment response by Apo E genotype
- CSF, serum and plasma biomarkers (Aß42, Aß42/40 ratio, total tau, p-tau-181, neurogranin, NfL, YKL-40, VILIP, SNAP-25, sTREM2, GFAP) at screening, week 24 and week 48 of the double-blind phase. CSF will be assessed in a subset of the study population (estimated n=50 active, n=50 placebo)

3.3.1 Exploratory Open-Label Extension Phase Objective

Exploratory Open-Label Extension Phase objective is to evaluate the safety and tolerability of BHV-4157 as measured by mortality rates, serious adverse events, adverse events, clinical safety laboratories, physical examinations and significant ECG changes.

4 ENDPOINTS

4.1 Co-Primary Endpoints

There are two primary efficacy endpoints:

- Within-participant change in ADAS-Cog 11 from baseline to week 48 of the double-blind phase, compared between the treatment group and the placebo group.
- Within-participant change in CDR-Sum of Boxes from baseline to week 48 of the double-blind phase, compared between the treatment group and the placebo group.

4.2 Secondary Endpoints

The secondary endpoints will measure the efficacy, and safety and tolerability of BHV-4157 as outlined below.

4.2.1 Efficacy

The efficacy of BHV-4157 will be assessed by the within-participant changes from baseline to week 48 of the double-blind phase, compared between the treatment group and the placebo group, on the following:

- Volumetric MRI (Quarc bilateral hippocampal volume)
- Neuropsychiatric Inventory (NPI) scores
- Alzheimer's Disease Cooperative Study (ADCS)-Activities of Daily Living (ADCS-ADL) scores
- Mini-Mental State Examination (MMSE) scores

4.2.2 Safety and Tolerability

The following safety and tolerability measures will be assessed for differences between the treatment group and the placebo group:

- Occurrence of mortality events
- Occurrence of serious adverse events (SAEs)
- Occurrence of adverse events (AEs)
- Clinical laboratory tests
- Vital signs
- Physical examinations
- ECGs
- Use of concomitant medications

4.3 Exploratory Endpoints

The following will be assessed:

- Efficacy of BHV-4157 assessed by the within-participant changes from baseline to week 48, compared between the treatment group and the placebo group, on Montreal Cognitive Assessment (MoCA) scores

- Efficacy of BHV-4157 assessed by the within-participant changes from baseline to week 48, compared between the treatment group and the placebo group, on performance using the AD Composite Score (ADCOMS), a composite outcome computed using 4 ADAS-Cog subscale items, 2 MMSE items, and the CDR Sum of Boxes (Wang et al., 2016)

- Efficacy of BHV-4157 assessed by the within-participant changes from baseline to week 48, compared between the treatment group and the placebo group, on volumetric MRI (bilateral lateral ventricles and whole brain volume)
- Efficacy of BHV-4157 assessed by the within-participant changes from baseline to week 48, compared between the treatment group and the placebo group, on a cognitive composite outcome computed using measures from the NACC Neuropsychological Test Battery [Craft Story 21 Recall (Immediate & Delayed); Benson Complex Figure (Copy & Delayed Recall); Multilingual Naming Test; Letter & Category Fluency; Trail Making Test A & B; Number Span Forward and Backward]
- Pharmacokinetics of BHV-4157 and riluzole in plasma
- Treatment response by APOE genotype (Qiu et al., 2019)
- CSF, serum and plasma biomarker panel (Aß42, Aß42/40 ratio, total tau, p-tau-181, neurogranin, NfL, YKL-40, VILIP, SNAP-25, sTREM2, GFAP) will be assessed at screening, week 24, and week 48. CSF will be assessed in a subset of the study population (estimated n=50 active, n=50 placebo)

4.3.1 Open-Label Exploratory Endpoints

The change in safety and tolerability measures including: (1) adverse events; (2) clinical laboratory tests; (3) vital signs; (4) physical examinations; (5) ECGs. Additional exploratory endpoint of evaluating long-term effects on clinical outcome measures.

4.4 CCI

CCI

5 ETHICS AND REGULATORY CONSIDERATIONS

5.1 Good Clinical Practice

This study will be conducted in accordance with:

- Principles of the Declaration of Helsinki (revised version of Fortaleza, Brazil October of 2013)
- Good Clinical Practice (GCP) guidelines, as defined by the International Conference on Harmonization (ICH) Guideline, Topic E6, the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) – Protection of Human Subjects and Part 56
- Institutional Review Boards (IRBs), Health Insurance Portability and Accountability Act (HIPAA), and all other applicable local regulatory requirements and laws

Study personnel involved in conducting this study will be qualified by education, training and experience to perform their respective task(s) in accordance with GCP.

5.2 Institutional Review Board

Institutional Review Boards and Research Ethics Boards must be constituted and their authority delegated through the institution's normal process of governance according to applicable State and Federal requirements for each participating location. Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment materials by an appropriate IRB registered with the Office for Human Research Protections (OHRP). The protocol will be submitted for approval to the appropriate IRB for each study site. The study will not commence at any site until written approval for investigational product release and approval to enroll is obtained from ADCS Regulatory Affairs.

The investigator must obtain approval from the IRB for all protocol amendments and, when warranted, changes to the informed consent document. Protocol and informed consent form

amendments can be made only with the prior approval of the ADCS and Sponsor. The investigator may not implement any protocol deviation except where necessary to eliminate an immediate hazard to study participants, or when change(s) involve only logistical or administrative aspects of the trial, i.e., change of monitor(s) or telephone number(s) (ICH 4.5.2). The investigator shall notify the IRB of deviations from the protocol or serious adverse events occurring at the site, in accordance with local procedures.

5.3 Informed Consent and HIPAA Compliance

No study-specific procedure will be undertaken on an individual participant until that participant or the participant's LAR has given written informed consent to take part in the study. The study partner must also participate in the consenting process.

It will be made clear to each potential participant, their LAR if applicable, and study partner that informed consent may be withdrawn at any time without needing to give a reason and that such withdrawal will not compromise the relationship between the participant and the Investigator nor the participant's future treatment.

Informed consent will be obtained in accordance with US 21 CFR 50.25 and ICH Good Clinical Practice. Applicable HIPAA privacy notifications will be implemented and HIPAA authorizations signed before protocol procedures are carried out. Information should be given in both oral and written form.

Consent forms must be in a language fully comprehensible to the prospective participants and/or their LARs, and study partners, and ample opportunity must be given to inquire about the details of the study. Prior to a participant's participation in the trial, the written informed consent form should be signed and personally dated by the participant or by the participant's LAR, and by the person who conducted the informed consent discussion. Participants or their LAR must be provided a copy of the signed ICF. Study partners may also be required to sign the informed consent prior to study participation at the discretion of the responsible IRB reviewing this research.

The consent for storage will include consent to access stored data, biological samples, and imaging data for secondary analyses. Consent forms will specify that DNA and biomarker samples are for research purposes only; the tests on the DNA and biomarker samples are not diagnostic in nature and participants will not receive results. MRI scan findings of clinical significance, determined by the site radiologist, can be shared with participants per site clinician discretion.

5.4 Participant Confidentiality | HIPAA

Information about study participants will be kept confidential and managed according to the requirements of HIPAA. Those regulations require a signed participant HIPAA Authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why

- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. Each site PI, under the guidance of his/her IRB, is responsible for ensuring that all applicable HIPAA regulations and state laws are met.

5.5 Potential Risks and Benefits Associated with this Study

5.5.1 Potential Risks

Risks associated with study participation are the potential for adverse reactions to the study medication (see Section 1.7.1), concomitant medications, invasive study assessments like blood draws and lumbar puncture, and risks related to the process of undergoing brain MRI scans and neuropsychological testing.

5.5.2 Potential Benefits

Participants in this study may experience an improvement in their AD symptoms, even though such improvement cannot be predicted with any surety. This study is expected to benefit the AD community by furthering the development of a new therapy and providing more information to those studying potential treatments for AD.

6 STUDY DRUG

6.1 Study Medication

The double-blind phase medication will be presented as one of the following:

- BHV-4157, 1 or 2 capsules (size 1) of 140 mg each, depending on assigned dose, and
- 1 or 2 capsules of matching Placebo

The Open-Label Extension phase medication will be:

- BHV-4157, 1 or 2 capsules (size 1) of 140 mg each

The study medication capsule should not be opened.

The study medication will be securely stored at the study site in accordance with the conditions specified on the label, separately from other drugs. The study medication may not be used for any purpose other than this study.

6.2 CCI

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CCI

6.3 CCI

CCI

6.4 Missed Doses

If a participant misses a dose of study drug and remembers within the same calendar day, the dose may be taken. If a participant misses a dose of study drug and does not remember until the next calendar day, the dose will be skipped (i.e., should not be made up) and dosing resumed at the normal dosing time for that calendar day.

6.5 Coding and Packing

Assignment of study medication kits to treatment groups will be done with an allocation ratio of 1:1 by a computer generated random sequence.

The study medication will be packaged in bottles. Each bottle will contain 35 capsules. An appropriate number of bottles (to provide study drug between visits) will be provided to the participant at each study visit (see Appendix 1 for Schedule of Study Visits).

Note: Each participant completing this study will take the study drug for 47 to 49 weeks in the double-blind phase, depending on scheduling of the End of Treatment Visit (week 48 ± 7 days) and an additional 47-49 weeks if they continue in the Open-Label Extension phase.

Note: If absolutely necessary, treatment duration may be longer due to the COVID-19 pandemic as detailed in the Schedule of Assessments and Events in Appendix 1. Under these circumstances, the sponsor medical monitor (or designee) should be consulted by the site investigator (or designee).

6.6 Blinding

This is a double-blind placebo-controlled trial. Treatments will be blinded to the participants and study personnel throughout the double-blind phase. Treatment blind will be maintained by use of matching placebo medication. In order to minimize unnecessary analysis of placebo blood PK samples, the bioanalytical scientist will be unblinded to treatment prior to unblinding

for the primary endpoint. Results of the blood concentration assay will be kept secure until database lock and unblinding for the primary endpoint.

Only in the case of an emergency, when knowledge of whether the participant has received the investigational product is essential for the clinical management or welfare of the participant, may the Investigator unblind a participant's treatment assignment. Procedures for emergency unblinding are initiated by contacting the ADCS Medical Monitor.

The interim analysis will be carried out by the unblinded safety biostatistics team and the report will be prepared for the DSMB. The DSMB will review all data pertaining to the CCI and will be unblinded. The DSMB will convey to the Study Steering Committee (SSC) whether or not the stopping criteria have been met.

The Study Steering Committee (SSC) that is overseeing the trial will receive the recommendation of the DSMB and have full access to data summaries provided to the DSMB. See Section 15 and the SSC Charter for additional details.

All participants entering the Open-Label Extension phase will not be blinded and will be on active treatment.

6.7 Randomization and Medication Ordering System

A stratified permuted block randomization procedure will be used with screening MMSE [moderate AD: 14 to 19; mild AD: 20 to 24] and Site as stratification factors.

The Investigator will use the ADCS EDC system to enter screening information on each participant. For those participants who qualify, the system will issue a medication kit number.

Participants will be randomized at the baseline visit, after screening is completed and it is determined that the participant is eligible for the study.

6.8 Labeling

Labels will be in accordance with all applicable regulatory requirements for the labeling of active pharmaceutical ingredients and with Annex 13 of GMP. Labels will contain the drug name, protocol number, date of manufacture, storage conditions and a caution statement that the drug is for clinical investigational use only.

6.9 Drug Accountability

The Investigator or his/her designated representatives will dispense study drug only to participants randomized to treatment in the study.

The Investigator (or, as appropriate, pharmacist/individual who is designated by the Investigator/institution) must maintain records of the delivery of the study medication to the trial site, the inventory at the site, the use by each participant, and the return to the drug distributor unless they are able to destroy on site.

At each visit, participants and their study partners should bring in all unused drug and empty or partially full containers. After the drug has been reviewed by the monitor, each site will destroy all unused study medication and empty or partially full containers collected from each participant, or return the study medication and containers to the drug distributor if they are unable to destroy on site.

If the study site needs to send drug overnight via certified and tracked courier where possible, and this is acceptable to the institution because a visit is absolutely not possible to be completed due to the COVID-19 pandemic, this is permissible per study. The sponsor should be consulted prior to shipping drug.

7 PARTICIPANT SELECTION AND CONCOMITANT MEDICATIONS

7.1 Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for enrollment:

1. Age 50 to 85 (inclusive) at screening.
2. Diagnosed with probable Alzheimer's disease dementia: Core clinical criteria in accordance with NIA/Alzheimer's Association Guidelines (see Appendix II).
3. Living in the community (includes assisted living facilities, but excludes long-term care nursing facilities).
4. Ambulatory, or able to walk with an assistive device, such as a cane or walker.
5. Participants must have a study partner who has frequent interaction with them (approximately >3-4 times per week), will be present for all clinic visits, and can assist in compliance with study procedures.
6. Female patients must be post-menopausal for at least 2 consecutive years or surgically sterile (bilateral tubal ligation, hysterectomy or bilateral oophorectomy) for at least 6 months prior to screening.
7. A modified Hachinski score of 4 or less at screening.
8. An MMSE score of 14 to 24, inclusive, at screening.
9. A brain MRI scan within 6 months of screening consistent with a diagnosis of Alzheimer's disease.
10. Body mass index (BMI) ≤ 40 kg/m^2 at screening.
11. Participants should be treated with a stable dosage regimen of FDA-approved AD medications (acetylcholinesterase inhibitors (AchEI) and/or memantine) for at least 3

months prior to screening. Participants should be expected to remain on a stable dosage regimen of these medications for the duration of the trial. The AD medication dose may be changed during the Open-Label Extension phase if needed, but it is preferred to wait until the Extension Phase Week 12 visit if possible.

a. Participants who are not being treated with FDA-approved AD medications at the time of screening, because they have contraindications to these medications, or because they have previously failed treatment with these medications, are also eligible for inclusion, if it is expected that they will not be treated with these medications for the duration of the trial.

12. Ability (patients and their study partners) to read, speak and understand English or Spanish to ensure compliance with cognitive testing and study visit procedures.

13. Provision of informed consent from the participant (or the participant's legally authorized representative (LAR) if unable to provide consent) and the study partner.

7.2 Exclusion Criteria

Patients meeting any of the following criteria must not be included in the study:

1. History of brain amyloid imaging (e.g., Amyloid Positron Emission Tomography scan) or cerebrospinal fluid results (e.g., based on tau and amyloid concentrations) that are not consistent with amyloidopathy or Alzheimer's disease. However, such tests may be repeated in order to determine eligibility, if discussed and approved by the Medical Monitor.

2. Use of prohibited medications as defined in Section 7.4.2.

3. Contraindication to MRI, including but not limited to:

   a. Clinical history or examination finding that, would pose a potential hazard for conducting an MRI, in the judgment of the principal investigator.

   b. Implant devices not compatible in the magnetic resonance environment, such as; AICDs; cochlear implants; cerebral aneurysm clips; implanted infusion pumps; implanted nerve stimulators; metallic splinters in the eye; other magnetic, electronic, or mechanical implants. Pacemakers are permitted only if labeled as conditional cardiac implantable electronic devices (CIEDs), have been approved for MRI use by the FDA, verified by the pacemaker's manufacturer as approved for MRI use, and determined to be suitable by the site's radiologist and principal investigator.

4. Current serious or unstable illness including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic, psychiatric, immunologic, or

hematologic disease or other conditions that, in the investigator's or sponsor's opinion, could interfere with the interpretation of safety and assessment of efficacy in this study.

5. Hepatic impairment defined as Child-Pugh class of A or more severe liver impairment.

6. Alanine aminotransferase (ALT/SGPT) values >1.5X the upper limit of normal (ULN) of the performing laboratory, aspartate aminotransferase (AST/SGOT) values >1.5X ULN, or total bilirubin values >1X ULN (participants with Gilbert's syndrome are allowed in the study).

7. Other neurodegenerative diseases and causes of dementias, including Parkinson's disease and Huntington's disease, vascular dementia, CJD (Creutzfeldt-Jakob disease), LBD (Lewy Body dementia), PSP (Progressive Supranuclear Palsy), AIDS (Acquired Immunodeficiency Syndrome), or NPH (normal pressure hydrocephalus).

8. Brain MRI at screening shows evidence of infection, tumor, cortical infarction, extensive white matter disease (Fazekas score > 2), or multiple lacunes in prefrontal or critical memory regions; inconclusive findings may be subject to review by the ADCS Imaging Core.

9. History of a major depressive episode within the past 6 months of screening.

10. History of schizophrenia diagnosis.

11. History of bipolar disorder.

12. History of seizures within 2 years of screening.

13. History of alcohol abuse or dependence or drug abuse in the past 5 years.

14. Insulin-dependent diabetes or uncontrolled diabetes with HbA1c value >8.0 %.

15. Hepatitis B, C, or HIV infection.

16. Clinically significant laboratory abnormalities that may influence study assessments as determined by the investigator.

17. Untreated or insufficiently treated hypothyroidism, vitamin B12 or folate deficiency.

18. ECG obtained during screening that, in the opinion of the investigator, is clinically significant with regard to the participant's participation in the study. Corrected QT interval (QTcF) must be evaluated using Fridericia's formula, and must not exceed 480 msec.

19. Cancer or a malignant tumor within the past 3 years, except patients who underwent potentially curative therapy with no evidence of recurrence for >3 years. Patients with stable prostate cancer or non-melanoma skin cancers are not excluded.

20. Participation in another clinical trial for an investigational agent and having taken at least one dose of study medication, unless confirmed as having been on placebo, within 12 weeks prior to screening. The end of a previous investigational trial is defined as the date of the last dose of an investigational agent.

21. Having received riluzole for more than 4 weeks prior to screening or with known tolerability difficulties to riluzole.

7.3 Concomitant AD Medication

Participants should be treated with a stable dosage regimen of FDA-approved AD medications (acetylcholinesterase inhibitors (AchEI) and/or memantine) for at least 3 months prior to screening. Participants should be expected to remain on a stable dosage regimen of these medications for the duration of the trial. The AD medication dose may be changed during the Open-Label Extension phase if needed, but it is preferred to wait until the Extension Phase Week 12 visit if possible.

Participants who are not being treated with FDA-approved AD medications at the time of screening, because they have contraindications to these medications, or because they have previously failed treatment with these medications, are also eligible for inclusion, if it is expected that they will not be treated with these medications for the duration of the double-blind phase of the trial.

7.4 Other Concomitant Medication

7.4.1 Permitted Concomitant Medications

The following concomitant medications are permitted:

- Medical foods and soy-based supplements, except as described in Section 7.4.2.
- Food supplements in general
- Vitamins in general
- Non-sedating antihistamines

The patient's condition **must be stable** while on the prescribed medications:

- Antidepressants starting at least two months prior to screening except the prohibited medications as described in Section 7.4.2.
- Beta-blockers used for cardiovascular reasons starting at least 2 months prior to screening

The following concomitant medications are permitted on an intermittent basis.

- Short to medium-acting benzodiazepines (estazolam, lorazepam, midazolam, oxazepam, temazepam, triazolam, alprazolam) taken no more than twice weekly
- Ramelteon (up to 8 mg), eszopiclone (up to 2 mg), zaleplon (up to 5 mg) or zolpidem tartrate (≤6.25 mg CR and ≤10 mg tablet) taken no more than twice weekly

- Sedating anti-allergy medications (e.g. diphenhydramine) taken no more than twice weekly

- Low dose anticonvulsant drugs used for non-epileptic indications which have been started and have been stable for at least 2 months prior to screening: Depakote 250 mg, Gabapentin 300 mg, Oxcarbazepine 600 mg, Pregabalin 100 mg, Lamotrigine 75 mg)

Any concomitant medications must be recorded in the eCRF, noting the name of medication, the dose, duration, and indication. However, any of these permitted concomitant medications used on an intermittent basis should not be taken less than 12 hours prior to any scheduled visits that include any cognitive tests.

7.4.2 Prohibited Concomitant Medications for double-blind phase but conditional for Open-Label Extension phase

The following concomitant medications are not permitted from screening through the end of the Randomized Double-Blind phase of the study. However, they are allowed per investigator judgement for the Open-Label Extension phase unless otherwise noted in 7.4.3.

- Tricyclic antidepressants (e.g.amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)
- Monoamine oxidase inhibitors (e.g. isocarboxazid, phenelzine, tranylcypromine, selegiline, rasagiline)
- Long-acting benzodiazepines
- Conventional and atypical antipsychotics (EXCEPT $\leq$ 50 mg/d of quetiapine and $\leq$ 0.5 mg/d of risperidone)
- Mood-stabilizing psychotropic agents (e.g. lithium salts)
- Prescription sedatives (e.g. barbiturates, methaqualone, meprobamate; EXCEPT ramelteon, eszopiclone, zaleplon and zolpidem tartrate under the condition described in Section 7.4.1.
- Psychostimulants (e.g. amphetamines, modafinil-related compounds like armodafinil)
- Dopamine agonists (e.g. apomorphine, pramipexole, ropinirole, rotigotine)
- Anticholinergics (e.g. benztropine mesylate, trihexyphenidyl HCL; EXCEPT inhaled ipratropium, inhaled tiotropium, oxybutynin, darifenacin, trospium, solifenacin and tolterodine)
- Anticonvulsant medications used to treat seizures or epilepsy which interfere with cognitive function or whose usage has not been stable for 6 months or longer (EXCEPT gabapentin at $\leq$ 300 mg QD for indications other than seizures)
- Chronic or regular use of opiate analgesics (e.g. morphine, codeine, hydromorphone, hydrocodone, meperidine, oxycodone)
- Immunosuppressive medications EXCEPT inhaled, topical, intra-nasal steroids, and low dose methotrexate for rheumatoid arthritis or psoriasis)
- Chemotherapeutic agents for malignancies
- Medical or recreational marijuana
- Glutamatergic agents (EXCEPT memantine)
- Hepatotoxic drugs (e.g. allopurinol, methyldopa, sulfasalazine) which may increase the

risk for hepatoxicity
- Axona® and Souvenaid® (EXCEPT when patients are using Axona® or Souvenaid® at the time of screening and continued use is advised by treating physician or Principal Investigator and is expected to continue throughout the study)

Participants who are actively being treated with low dose acetylsalicylic acid (ASA) may undergo lumbar puncture, at the discretion of the investigator. Participants who are actively being treated with dual antiplatelet therapy or with any anticoagulation medications (e.g. heparin, warfarin, thrombin inhibitors, Factor Xa inhibitors) should **not** undergo lumbar puncture. Platelet counts should be >100,000, and PTT and INR levels checked and in normal range before the lumbar puncture is performed. The ADCS Medical Monitor should be contacted if there are any questions.

If, during the clinical study, the administration of a non-permitted concomitant medication becomes necessary, the Medical Monitor must be contacted to determine if the participant needs to be prematurely discontinued from active treatment (see Section 10).

7.4.3 Prohibited Medications, both in double blind and 0pen-label extension phases .

The following concomitant medications are neither permitted in the double blind nor the open-label extension phase of the Study:

- Hepatotoxic drugs (e.g., allopurinol, methyldopa, sulfasalazine) which may increase the risk for hepatoxicity

- Sensitive and moderately sensitive substrates of the CYP2B6, CYP2C8, CYP2C9, and CYP2C19 enzymes (please see the table below).

Enzyme	**Sensitive Substrates**	**Moderately Sensitive Substrates**
CYP2B6	Bupropion	efavirenz
CYP2C8	Repaglinide	montelukast, pioglitazone, rosiglitazone
CYP2C9	Celecoxib	glimepiride, phenytoin, tolbutamide, warfarin
CYP2C19	S-mephenytoin, omeprazole	diazepam, lansoprazole, rabeprazole, voriconazole

The following medications are prohibited at least 14 days prior to randomization or 5 half-lives (whichever is longer) prior to randomization, and during the double-blind and Open-Label Extension phases of the study, due to the potential for drug interactions:

- Strong to moderate CYP1A2 inhibitors, such as amiodarone, cimetidine, and ciprofloxacin which may increase the risk of riluzole-associated adverse events (See Appendix III for detailed medication listing)

- Chronic use of strong to moderate CYP1A2 inducers, such as carbamazepine, modafinil and omeprazole, which may result in decreased efficacy (See Appendix III for detailed medication listing)

8 STUDY PROCEDURES

8.1 Study Visits

The schedule of study visits and procedures to be performed at each visit are outlined below and a table can be found in Appendix 1.

Every effort should be made to conduct the study visits as planned. However, due to concerns related to the COVID-19 pandemic, study participants may be unable to come into the office for their study scheduled visit, in order to minimize any potential risks to study participant safety and to comply with governmental and local institutional guidance (e.g., study site has a policy that a clinical research visit must be delayed). Under these circumstances, the investigator should contact the sponsor medical monitor (or designee) to discuss the most appropriate course of action. For visits other than the Week 48 visit, remote safety visits will be allowed on a case by case basis, if a participant is unable to come to the site for evaluation including physical examination or if safety labs cannot be performed due to the COVID-19 pandemic. The site investigator should discuss the specific requirements for the remote safety visit with the Sponsor Medical Monitor, which will be based on the study visit number and the clinical status of the participant, with consideration of their trial compliance to study medication, previous labs and other risk factors. Shipping of study drug from the site to the participant via overnight tracked and certified courier, where possible will also be allowed.

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8.1.1 Screening (within 42 days prior to baseline)

Participants whom the Investigator considers to be appropriate for the study, will have the study explained to them, their LAR if applicable, and their study partner by the Investigator or his/her designee and will be given a copy of the written Informed Consent Form (ICF). When they have had sufficient time to study this information and the opportunity to ask any questions they wish, they will be invited to give their consent to participation by signing the ICF. The study partner

may also be required to sign the ICF at the discretion of the responsible IRB reviewing this research. Participants who are willing to participate in the CSF sub-study will so indicate in the section provided on the ICF.

Once the participant or LAR (and study partner if required) have given consent, the following procedures will be undertaken during the screening period.

- Confirmation of probable Alzheimer's disease using the NIA/Alzheimer's Association Guidelines (see Appendix II)
- MMSE (score between 14 to 24, inclusive)
- Documentation of demographics, medical history, smoking habits and education
- Modified Hachinski ischemic test (score of 4 or less)
- Neurological exam
- Physical examination
- Vital signs (sitting blood pressure, pulse, temperature, respiration rate)
- Weight
- Height
- Documentation of concurrent pathologies and concomitant treatment
- Documentation of adverse events from time of consent. Adverse events that occur prior to initiation of study drug will be documented as medical history.
- Blood samples for:
    - Clinical safety laboratory tests (hematology and serum chemistry, as listed in Section 8.2).
    - HIV, HBsAg, HCV antibody
    - ApoE (e4 +/-) genotyping
- Urinalysis (see Section 8.2)
- Resting 12-lead ECG
- Volumetric MRI per protocol imaging requirements;
    - If a participant has not had an MRI performed within 6 months of screening (i.e., within 6 months from the date of informed consent), then an MRI must be performed as part of the screening requirements for this study, per the imaging protocol, and should be one of the last screening procedures performed to determine final eligibility in order to prevent participants from undergoing unnecessary MRIs.
    - If a participant has had an MRI within 6 months of screening (i.e., within 6 months from the date of informed consent) but the MRI does not follow the study-specific imaging protocol, that MRI can be used to help determine eligibility; however, another MRI must be performed per the imaging protocol, and must occur as close to, and prior to, the baseline visit, after all other eligibility criteria have been confirmed.
- Lumbar puncture*
- Post lumbar puncture safety telephone follow-up (1 to 3 days after lumbar puncture)
- Sheehan Suicidality Tracking Scale

*NOTE: Participants who have consented to participate in the CSF sub-study should undergo a lumbar puncture to obtain samples of CSF no more than 14 days prior to their first dose of study

drug at baseline. The participant's vitals should be assessed before and after the procedure, or per standard local practice. INR, PT, PTT and platelets should be assessed at the site's local laboratory at least 24 hours, and within normal range, prior to the lumbar puncture. The lumbar puncture should be done ***after*** the MRI scan *if* performed on the same day. If the lumbar puncture is performed on a **separate day** from the MRI and occurs **before** the MRI, then there must be at least a 3-day window between the lumbar puncture and the MRI. If the lumbar puncture is performed on a separate day from the MRI and occurs **after** the MRI, then there is no window (waiting period) between the MRI and lumbar puncture. Both the lumbar puncture and vMRI should occur after all other eligibility criteria have been confirmed.

Following completion of all screening assessments, results for participants who meet all inclusion and none of the exclusion criteria will be submitted via the ADCS EDC for central confirmation of eligibility. If confirmed to be eligible, permission to randomize will be issued and the participant may be randomized.

Randomization must occur at the baseline visit; otherwise, the participant will be considered a screen failure.

Re-screening

A single full re-screen (re-consent participant, assign new Participant ID and perform all screening assessments) may be conducted more than 14 days after the last assessment of a screening failure.

If the participant is failed again at re-screening, further re-screening and its minimum interval from the previous one, may be done if the PI and Central Review Medical Monitor are in agreement to do so.

For re-screening, vMRI taken at the 1st screening (screening failure) can be used if it will be less than 3 months old at the time of randomization. Otherwise, vMRI needs to be repeated.

If the participant is participating in the CSF sub-study and the lumbar puncture was done before screening failure, please ask ADCS if lumbar puncture should be re-taken when the participant is re-screened and randomized.

8.1.2 Baseline (Week 0)

At baseline, eligible participants will be randomized into the study. Each will undergo the following procedures **prior** to first dose of study medication:

- Verification of Inclusion/Exclusion criteria
- Randomization in EDC
- Physical exam
- Vital signs (sitting blood pressure, pulse, temperature, respiration rate)
- Weight
- Documentation of concomitant treatment
- Documentation of adverse events. Adverse events that occur prior to initiation of study drug will be documented as medical history.

- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 8.2).
  - Pharmacokinetics in plasma
  - Biomarker/banking
- Urinalysis (see Section 8.2)
- Sheehan Suicidality Tracking Scale
- ADAS-Cog 11
- CDR-SOB
- NPI
- ADCS-ADL
- Neuropsychological Test Battery
  - Craft Story 21 Recall (Immediate and Delayed)
  - Benson Complex Figure
  - Multilingual Naming Test (MINT)
  - Letter & Category Fluency
  - Trail Making Test A&B
  - Number Span Test
- MMSE
- Montreal Cognitive Assessment (MoCA)
- Research Satisfaction Survey

First dose of study medication will be given in the clinic at any time after completion of all of the above.

At this visit, all participants will receive a supply of study drug with instructions on how to take it. Participants will be given an appointment to return at week 4 (± 7 days).

8.1.3 Week 2 (± 3 days)

Participants will receive a phone call during Week 2 from site study personnel in order to assess study drug tolerability. If tolerable, then the participant will be instructed to proceed with dose escalation. The following procedures must occur:

- Documentation of concomitant treatment
- Documentation of adverse events
- Instruction on drug dosing regimen

8.1.4 Week 4 (± 7 days)

All participants returning for week 4 will undergo the following procedures:

- Physical exam
- Vital signs (sitting blood pressure, pulse, temperature, respiration rate)
- Weight
- Documentation of concomitant treatment

- Documentation of adverse events
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 8.2)
  - Pharmacokinetics (in plasma)
- Urinalysis (see Section 8.2)
- Sheehan Suicidality Tracking Scale

At each visit, participants will receive a supply of study drug with instructions on how to take it. Participants will be given an appointment to return in 4 weeks (± 7 days).

8.1.5 Week 8 (± 7 days)

All participants returning for week 8 will undergo the following procedures:

- Physical exam
- Vital signs (sitting blood pressure, pulse, temperature, respiration rate)
- Weight
- Documentation of concomitant treatment
- Documentation of adverse events
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 8.2)
  - Pharmacokinetics (in plasma)
- Sheehan Suicidality Tracking Scale

At this visit, participants will receive a supply of study drug with instructions on how to take it. Participants will be given an appointment to return in 4 weeks (± 7 days).

8.1.6 Week 12 (± 7 days)

All participants returning for week 12 will undergo the following procedures:

- Physical exam
- Vital signs (sitting blood pressure, pulse, temperature, respiration rate)
- Weight
- Documentation of concomitant treatment
- Documentation of adverse events
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 8.2)
  - Pharmacokinetics (in plasma)
- Urinalysis (see Section 8.2)
- Resting 12-lead ECG
- Sheehan Suicidality Tracking Scale
- ADAS-Cog 11
- CDR-SOB
- Research Satisfaction Survey

At this visit, participants will receive a supply of study drug with instructions on how to take it. Participants will be given an appointment to return in 12 weeks (± 7 days).

8.1.7 Week 24 (± 7 days)

All participants returning for week 24 will undergo the following procedures:

- Physical exam
- Vital signs (sitting blood pressure, pulse, temperature, respiration rate)
- Weight
- Documentation of concomitant treatment
- Documentation of adverse events
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 8.2)
  - Pharmacokinetics (in plasma)
  - Biomarker/bio banking
- Urinalysis (see Section 8.2)
- Resting 12-lead ECG
- Lumbar puncture* (± 14 days of week 24)
- Sheehan Suicidality Tracking Scale
- ADAS-Cog 11
- CDR-SOB
- Volumetric MRI (± 14 days of week 24)
- NPI
- ADCS-ADL
- MMSE
- MoCA
- Research Satisfaction Survey

At this visit, participants will receive a supply of study drug with instructions on how to take it. Participants will be given an appointment to return in 12 weeks (± 7 days).

*NOTE: Participants who have consented to participate in the CSF sub-study will undergo a lumbar puncture for CSF within 14 days prior to this visit. Plasma samples for PK for this subset of participants should be drawn at the time of lumbar puncture. The participant's vitals should be assessed before and after the procedure, or per standard local practice. INR, PT, PTT and platelets should be assessed at the site's local laboratory at least 24 hours, and within normal range, prior to the lumbar puncture. The lumbar puncture should be done ***after*** the MRI scan *if* performed on the same day. If the lumbar puncture is performed on a **separate day** from the MRI and occurs **before** the MRI, then there must be at least a 3-day window between the lumbar puncture and the MRI. If the lumbar puncture is performed on a **separate day** from the MRI and occurs **after** the MRI, then there is no window (waiting period) between the MRI and lumbar puncture. If a participant in the CSF sub-study is terminating early, they do not need to undergo this lumbar puncture. However, every effort will be made to encourage the participant's ongoing voluntary

participation and to explain that CSF collection may provide informative information in the future for the field of AD.

8.1.8 Week 36 (± 7 days)

All participants returning for week 36 will undergo the following procedures:

- Physical exam
- Vital signs (sitting blood pressure, pulse, temperature, respiration rate)
- Weight
- Documentation of concomitant treatment
- Documentation of adverse events
- Sheehan Suicidality Tracking Scale
- ADAS-Cog 11
- CDR-SOB
- Research Satisfaction Survey

At each visit, participants will receive a supply of study drug with instructions on how to take it. Participants will be given an appointment to return in 12 weeks (± 7 days).

8.1.9 Week 48 or Early Termination (± 7 days)

Every effort should be made to conduct the Week 48 visit and maintain the +/- 7 day window. However, due to concerns related to the COVID-19 pandemic, the Week 48 visit window may be modified beyond the +/- 7 day window, in order to minimize any potential risks to study participant safety and to comply with governmental and local institutional guidance (e.g., study site has a policy that a clinical research visit must be delayed). Under these circumstances, the visit window may be extended (up to a maximum treatment duration of 60 weeks), but every attempt should be made to conduct the visit as close to the date the visit is due as possible. If the visit window is modified, participants should be evaluated remotely (e.g., via phone) at the time of the scheduled Week 48 visit to perform and document appropriate safety assessments. Study medication may be sent to the participant via tracked courier. For any such cases, the investigator should discuss the specific circumstances of each case with the sponsor medical monitor (or designee) who must approve the request prior to any modification of the visit window.

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All participants returning for week 48 will undergo the following procedures:

- Physical exam
- Vital signs (sitting blood pressure, pulse, temperature, respiration rate)
- Weight
- Documentation of concomitant treatment
- Documentation of adverse events
- Blood samples for:
    - Safety laboratory tests (hematology and serum chemistry, as listed in Section 8.2)
    - Pharmacokinetics* (in plasma)
    - Biomarker/banking
- Urinalysis (see Section 8.2)
- Resting 12-lead ECG
- Lumbar puncture* (± 14 days of week 48)
- Post lumbar puncture safety telephone follow-up (1 to 3 days after lumbar puncture)
- Sheehan Suicidality Tracking Scale
- ADAS-Cog 11
- CDR-SOB
- Volumetric MRI (± 14 days of week 48)
- NPI
- ADCS-ADL
- Neuropsychological Test Battery
    - Craft Story 21 (Immediate and Delayed)
    - Benson Complex Figure
    - Multilingual Naming Test (MINT)
    - Letter & Category Fluency
    - Trail Making Test A&B
    - Number Span Test
- MMSE
- Montreal Cognitive Assessment (MoCA)
- Research Satisfaction Survey

*NOTE: Participants who have consented to participate in the CSF sub-study will undergo a lumbar puncture for CSF within 14 days prior to this visit. Plasma samples for PK for this subset of participants should be drawn at the time of lumbar puncture. The participant's vitals should be assessed before and after the procedure, or per standard local practice. INR, PT, PTT and platelets should be assessed at the site's local laboratory at least 24 hours, and within normal range, prior to the lumbar puncture. The lumbar puncture should be done ***after*** the MRI scan ***if*** performed on the same day. If the lumbar puncture is performed on a **separate day** from the MRI and occurs **before** the MRI, then there must be at least a 3-day window between the lumbar puncture and the MRI. If the lumbar puncture is performed on a **separate day** from the MRI and occurs **after** the MRI, then there is no window (waiting period) between the MRI and lumbar puncture. If a participant in the CSF substudy is terminating early, they do not need to undergo this lumbar puncture. However, every effort will be made to encourage the participant's ongoing voluntary participation and to explain that CSF collection may provide informative information in the future

for the field of AD. Participants will be given an appointment to return in 4 weeks (± 7 days) unless this serves as their Early Termination visit.

8.1.10 Week 52 Safety Follow-up (± 7 days)

All participants returning for week 52 (who are not going into the Open-Label Extension phase) will undergo the following procedures after the Week 48 visit is completed in person:

- Physical exam
- Vital signs (sitting blood pressure, pulse, temperature, respiration rate)
- Weight
- Documentation of concomitant treatment
- Documentation of adverse events
- Blood samples for safety laboratory tests (hematology and serum chemistry, as listed in Section 8.2)
- Resting 12-lead ECG
- Sheehan Suicidality Tracking Scale

8.1.11 Unscheduled Visit

Documentation of concomitant medication, adverse events, and vital signs will be collected at all unscheduled visits, and additional clinical safety laboratories may be completed at the discretion of the PI or at the request of the medical monitor. Participants returning to conduct an unscheduled visit outside of the protocol's visit schedule may have missing or additional study procedures performed by site personnel.

8.1.12 Open-Label Extension Phase (as applicable)

The Extension Phase is an optional open-label 48-week treatment phase. The investigator will be responsible for evaluating any major changes in the participant's status to determine their participation in the open-label extension. This should be based on the status of the participant at the end of the double-blind phase, the participant's risk-benefit profile as determined by the site PI, the consent of the participant, and the integrity of the trial.

If the participant has completed the double blind treatment phase prior to the Open-Label Extension Phase being approved at their study center, they can re-consent and start the study as long as the investigator determines that open-label treatment offers an acceptable risk-benefit profile for the individual. Once the study site is open for recruitment for the Open-Label extension, participants that completed the study prior will have up to 12 weeks to enroll in the Open-Label study.

When sites have opened for recruitment for the Open-Label Extension Phase, participants completing the double-blind treatment phase must go directly from the Week 48 visit into the Extension Phase if they choose and are eligible to continue.

- Participants who are completing the double-blind treatment phase may directly enter the Open-Label Extension phase. These participants should not complete the follow-up safety

visit at Week 52 (of the double-blind treatment phase). Instead, these participants should continue directly into the Open-Label Extension phase starting at Week 48 (of the double-blind treatment phase). The Week 48 visit will also serve as the Baseline visit in the Extension Phase for participants who are going directly from the double-blind treatment phase to the OLE. Thereafter, participants will undergo visits at Week 4, Week 8, Week 12, and then every 12 weeks of the Extension Phase as outlined in Table 3 (Schedule of Assessments/Time & Events- Extension Phase).

- Participants who previously completed the double-blind treatment phase prior to the Open-Label Extension phase of the study being open for recruitment at their study center, may also enter the Open-Label Extension (OLE) phase.
    - For participants who will have been off of the study drug for less than or equal to 4 weeks, the subject should come into the investigative site for an Abbreviated Drug Dispensation Visit (also "Abbreviated OLE Baseline Visit"), at which time any major medical or medications changes will be reviewed prior to dispensing riluzole. In this case, most procedures from the Week 48 visit will also serve as the OLE Phase Baseline visit, as outlined in Table 3 (Schedule of Assessments/Time & Events-Extension Phase). Thereafter, participants will undergo visits at Week 4, Week 8, Week 12, and then every 12 weeks of the OLE Phase.
    - For participants who have been off the study drug for greater than 4 weeks, these participants should be re-assessed and re-consented by the PI during an OLE Baseline Visit. From the date that the Open-Label Extension is open for recruitment at the study site, these participants that completed the study prior will have up to approximately 12 weeks to complete the OLE Baseline Visit. Thereafter, participants will undergo visits at Week 4, Week 8, Week 12, and then every 12 weeks of the OLE phase as outlined in Table 3 (Schedule of Assessments/Time & Events-Extension Phase). All previous completers of the double-blind phase will have a 12-week window of opportunity to baseline into the OLE, regardless of their date of double-blind phase completion. In the event sites open for OLE recruitment, then close due to COVID-19 before enrolling all prior completers, exceptions to the 12-week window will be considered on a case-by-case basis, following discussion with the Sponsor Medical Monitor:

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- As with the double-blind phase, certain provisions may be implemented, in order to minimize potential hazards to study participants due to COVID-19. These provisions may allow alternatives to in-person study visits and include but are not limited to the following: conducting remote visits via phone/telemedicine video, focusing on safety assessments during remote visits, performing safety labs via local labs or professional in home

phlebotomy vendors, and shipping study medication to study subjects if needed. Any potential issues should be discussed with the Sponsor and will be addressed on an individualized basis.

  - OLE visits may be completed remotely, if necessary due to COVID-19. However, participants should not be on study drug for greater than 24 weeks without completing an in-person visit. For these participants, IP should be held or the participant discontinued.

- Participants who early-terminated from the double-blind phase trial or discontinued the study drug for any reason will not eligible for enrollment into the OLE phase.
- All participants must have their Week 48 visit in person prior to enrolling in the OLE phase. (Due to COVID-19, the timing of this visit may be delayed)

All participants entering the OLE phase will start with one capsule of BHV-4157 per day and titrate to two capsules per day after week two. This will be done so that all participants will be on open-label medication and will safely continue from either active BHV-4157 or placebo.

All participants in the Open-Label Extension phase are planned to undergo a termination visit two weeks after the last dose of study drug.

8.2 Laboratory Safety Assessments

Clinical Safety Laboratory tests will be performed by a Central Laboratory. Assessments include the following:

Hematology:

Hemoglobin, hematocrit, platelet count, RBC, WBC, differential count and absolute neutrophil count

Chemistry:

Sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorous, bicarbonate, CPK, total protein, albumin, direct bilirubin, indirect bilirubin, total bilirubin, glucose, creatinine, BUN, uric acid, total cholesterol, LDL, HDL, triglycerides (lipids collected only during double-blind phase), B12 (at screening only), folate (at screening only)

Urinalysis:

pH, specific gravity, protein, glucose, ketones, urobilinogen, bilirubin, blood

An approximate blood volume of 9.5 ml at screening and 7 mL at subsequent study visits (baseline, week 4, week 8, week 12, week 24, and week 48, Open-Label Extension phase week 4, week 8, week 12, week 24, week 36, and week 48), will be collected for serum chemistry and hematology analyses. If vitamin B12 is below normal and the Investigator thinks it necessary, an additional blood (approximately 5 ml) may be taken to measure serum methylmalonic acid levels at another visit during screening period.

Urine will be collected for urinalysis at screening, baseline, week 4, week 12, week 24 and week 48, and Open-Label Extension phase week 4, week 8, week 12, week 24, and week 48.

The Central Laboratory will provide the investigational sites with all appropriate materials for specimen collection, sample processing, packaging and shipping. Full details of sampling (blood and urine), sample preparation and storage methods will be given in the laboratory manual.

If a participant is unable to come in to the study site and needs to have safety labs conducted locally, this is acceptable. The study site should provide the participant or local laboratory with a requisition and should collect the results. A home phlebotomist may also be an option for participants if needed.

8.3 Pharmacokinetic Assessments

A plasma sample for pharmacokinetic (PK) should be collected at baseline, week 4, week 8, week 12, week 24, and week 48 of the double-blind phase of the trial. Participants should take their dose at their routine time on the days of these visits. Date and time of last dose should be collected in case report forms for entry into the EDC system. *Participants who are able to be scheduled for a morning visit should be instructed to hold their dose of study drug that morning until after a PK trough sample is obtained, if possible and appropriate in the judgment of the investigator.*

PK samples should be drawn if there are any SAEs that could possibly be drug-related or severe AEs that could be drug-related.

In addition, for participants undergoing lumbar puncture, plasma samples for PK should be drawn at the time of lumbar puncture for Week 24 and Week 48 visits for the double blind placebo phase. Date and time of last dose should be collected in case report forms for entry into the EDC system.

There is no PK sampling during the OLE phase.

8.4 Physical and Neurological Examination

A physical examination will be performed by a medically qualified professional at every study visit. A review of the major body systems will be performed and vital signs will be assessed. A neurological examination will only be performed at screening and will include assessment of motor strength, sensory, deep tendon, tremor, cerebellar, cranial, and mental status.

8.5 Genotyping

ApoE (e4 +/-) genotype is associated with the risk and age of onset of AD. ApoE genotyping will be performed at screening. The blood collection will total approximately 10 mL. Results of ApoE genotyping will be used in exploratory subgroup analyses to explore the relationship between ApoE genotype clinical course and response to treatment.

If a participant has agreed to allow his/her sample to be banked, then the DNA sample will be stored at the UCSD and used for additional genetic testing. Samples will be de-identified prior to being shared with outside investigators to preserve the confidentiality of participants. Participants can request in writing any time to have their samples destroyed. Results of this testing are for research purposes only and will not be disclosed to the participant or study partner.

8.6 Electrocardiogram

A standard 12-lead resting ECG will be performed during screening, week 12, week 24, and week 48 of the double-blind phase, and week 12, week 24, and week 48 of the Open-Label Extension phase. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the eCRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormalities on ECGs recorded after administration of the investigational product will also be documented as AEs and entered on the AE page of the eCRF. Clinically significant abnormalities on ECGs prior to administration of the investigational product, will be recorded as medical history.

8.7 vMRI Assessments

Brain structural change is seen in normal aging, but is accelerated in neurodegenerative disease, including AD. Atrophy in AD arises from neuron and synapse loss that begins in the entorhinal cortex. The pathology then spreads throughout the limbic regions of the temporal lobe, including the hippocampal formation. Subsequently, neuron loss and atrophy is observed throughout neocortical association areas in temporal, parietal and frontal lobes.

vMRI allows the *in vivo* assessment of brain structure volume and provides a measure of atrophy rate. Results from vMRI studies suggest that the patterns of atrophy in AD, which mirror the pathological progression of the disease, can reliably be detected and tracked across time. Atrophy of the medial temporal lobe, including hippocampus and entorhinal cortex, has long been described in vMRI studies of AD. Hippocampal volume derived from MRI correlates with histological hippocampal volume and degree of neuronal loss and AD pathology, and entorhinal cortical thickness change appears to be an early and sensitive indicator of neurodegeneration associated with AD (Holland et al., 2009; Jack et al., 2004). Longitudinal MRI measures of regional and whole-brain volumetric change provide a valuable complement to cognitive measures in that they are not influenced by temporary symptomatic improvements, and they provide an early index of the study drug's ability to reach the target organ and have an effect on AD-related atrophy.

Participants will undergo vMRI scans of the brain at screening, week 24 and week 48 (and Extension Phase baseline and week 48) in order to assess for changes in brain volumes that may be associated with clinical change due to treatment with BHV-4157.

Volumetric MRI scans will use the same imaging protocol, which will include a localizer scan, a 3D T1- weighted sagittal acquisition (MPRAGE or IR-SPGR), a T2-weighted FLAIR axial acquisition, a T2* gradient recalled echo axial acquisition for magnetic susceptibility, and a diffusion weighted axial acquisition to assess for restricted diffusion.

Images will be checked for image quality and adherence to scanning protocols. 3D T1-weighted datasets passing quality checks will be corrected for spatial distortion and for intensity variation. Screening and follow-up datasets for each participant will be spatially registered to one another using rigid-body registration followed by nonlinear registration and neuroanatomic parcellation to quantify whole-brain and subregional volumetric change on a patient-by-patient basis.

The local MRI results will determine eligibility for each participant in the double blind treatment phase of the trial when the PI will confirm if MRI results are consistent with AD, meet the specified inclusion criteria, and do not have exclusionary findings as defined by the protocol. It is the responsibility of the PI to make this determination following review of the MRI, and to sign as well as date the local radiology report or the PI's own brain MRI written evaluation to acknowledge their review. The PI is at liberty to consult with a local neuroradiologist, however there is no requirement for a formal MRI read from a neuroradiologist. The ADCS Medical Safety team, or ADCS Imaging core are available to address any questions surrounding MRI eligibility. If there are safety concerns identified on this MRI, the PI should communicate with the participant's Primary Care Physician and consult with ADCS Medical Monitor, ADCS Director, and ADCS Imaging Core.

Whole brain volume (WBV, excluding cerebellum), bilateral ventricular volume and bilateral hippocampal volume will be measured. Quantitative anatomical regional change (Quarc) will be used as the computational MR image processing application. Detail for the statistical computations is given in the Statistical Analytical Plan (SAP).

If performed on the same day as a lumbar puncture, the vMRI should be conducted before the lumbar puncture. Otherwise, at least a 3-day window between vMRI and the lumbar puncture is required. Scanners that have passed the study's qualification procedures will be used. Participants must be scanned by the same scanner throughout the study.

Participants with a contraindication to MRI at the time of screening are deemed ineligible to participate in this study. Participants may continue to participate on the study if they have already been randomized but develop a contraindication to MRI during the course of the study.

8.8 CSF, Serum and Plasma Sub-study Assessments

CSF, serum and plasma will be taken at screening within 14 days prior to first dose of study drug and within 14 days prior to weeks 24 and 48 to measure biomarkers (e.g., Aß42, Aß42/40 ratio, total tau, p-tau-181, neurogranin, NfL, YKL-40, VILIP, SNAP-25, sTREM2, GFAP) in the double-blind treatment phase of the trial. For the OLE phase, serum and plasma will be taken at weeks 24 and 48. These samples will be banked at a central biorepository for future exploratory biomarker analyses.

CSF samples should be collected at the same time of day, either morning (between 8 and 10AM) or afternoon (between 1 and 3PM). The first lumbar puncture must be conducted prior to initiation of study drug. Plasma samples for PK should be drawn at the time of lumbar puncture. Date and time of doses on the day of lumbar puncture and day prior should be collected in case report forms, for entry into the EDC system.

The estimated 100 participants (n=50 active, n=50 placebo) who are within the sentinel cohort of the double-blind treatment phase of the trial will constitute the study sample for the CCI andwill also have the opportunity to participate in a CSF, serum, and plasma sub-study, with samples drawn in the screening period and at week 24, with the option for a third sampling timepoint at week 48.

In addition to the sentinel sub-study participants, other consenting trial participants will be approached to undergo a blood draw to provide serum and plasma biomarkers. For CSF, consenting participants will undergo a lumbar puncture at screening within 14 days prior to first dose of study drug and within 14 days prior to week 48 to measure the CSF biomarkers in the double-blind treatment phase of the trial.

Anti-platelet and anticoagulant medications and lumbar puncture are addressed above in in (Prohibited Concomitant Medications, Section 7.4.2). Participants who are taking anticoagulants or dual antiplatelet drugs are excluded from the CSF sub-study.

Details of the CSF sampling are contained in the Study Procedures Manual.

The unused portion of CSF may be transferred to the National Cell Repository for Alzheimer's Disease (NCRAD) for future research. Participants will be given the choice to allow such sample retention and further investigation of their CSF.

9 STUDY-SPECIFIC INSTRUMENTS

9.1 Cognitive Measures

9.1.1 Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog 11)

The ADAS-Cog 11 (Rosen, Mohs, & Davis, 1984) is a structured scale that evaluates memory (word recall, word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing a letter in an envelope) and constructional praxis (copying geometric designs). Ratings of spoken language, language comprehension, word finding difficulty, and ability to remember test instructions are also obtained. The test is scored in terms of errors, with higher scores reflecting poorer performance and greater impairment. Scores can range from 0 (best) to 70 (worse).

9.1.2 Mini-Mental State Examination (MMSE)

The MMSE is a frequently used screening instrument for Alzheimer's disease drug trials. It evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two intersecting pentagons (Folstein, Folstein, & McHugh, 1975). A lower score indicates more cognitive impairment. The highest (best) score is 30.

9.1.3 Montreal Cognitive Assessment (MoCA)

The MoCA is a brief mental status exam which was designed to be more sensitive to mild cognitive impairment and early dementia than the MMSE (Nasreddine et al., 2005). It assesses numerous cognitive domains, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Like the MMSE, the highest (best) score is 30. Administering both the MoCA and the MMSE in this trial will allow comparisons of the utility within the setting of a clinical trial.

9.1.4 Neuropsychological Test Battery (NTB)

The neuropsychological battery from the Uniform Data Set (v3.0 – Form C2) of the National Alzheimer's Coordinating Center (NACC) (Weintraub et al., 2009) will be administered to provide a more detailed assessment of cognition. The battery includes brief measures of attention, processing speed, executive function, episodic memory, and language. Exploratory analyses will evaluate the treatment effects on a composite measure of this neuropsychological battery between baseline and endpoint . As described in the manual for test administration and scoring (Version 3.0, March 2015), Form C2 of the NACC UDS battery includes the following measures:

9.1.4.1 Craft Story 21 Recall (Immediate and Delayed)

This is a measure of verbal episodic memory (Craft et al., 1996). A brief story is read to the participant, who is then asked to retell it immediately from memory. The primary measure of performance is the number of story units recalled. Delayed recall of the story is assessed 20 minutes after immediate recall. Other neuropsychological measures are administered during the delay interval (Range: 0-25 for each recall trial).

9.1.4.2 Benson Complex Figure Copy & Recall

This test is a simplified form of the Rey-Osterrieth Complex Figure (Possin, Laluz, Alcantar, Miller, & Kramer, 2011). The purpose is to assess visuoconstructional and visual memory functions. In this test, the participant is presented with a figure composed of geometric shapes. The participant is then asked to reproduce (i.e., copy) the figure on the same page. The accuracy of each shape and its placement are recorded. The primary measure of performance is the total score for copying the figure (Range: 0-17). Approximately 10-15 minutes after the participant copies the figure, visual memory is assessed by asking the participant to draw the figure again, from memory, on a blank page. The accuracy of each shape and its placement are recorded. The primary measure of performance is the total score for the delayed drawing of the Benson figure (Range: 0-17).

9.1.4.3 Multilingual Naming Test (MINT)

The MINT is a test of visual confrontation naming (Ivanova, Salmon, & Gollan, 2013). Participants are required to identify (i.e., name) line drawings of objects. If the initial response is incorrect, semantic and/or phonemic cues are provided, as appropriate. Items are counted as correct if spontaneously named after semantic cuing (Range: 0-32).

9.1.4.4 Trail Making Test (Trails A and B)

The Trail Making Test is a test of processing speed and executive function. Trails A consists of 25 circles numbered 1 through 25 distributed over a white sheet of paper. The participant is instructed to draw a line to connect the circles in ascending numerical order as quickly as possible (150 second maximum). Trails B consists of 25 circles containing either numbers (1 through 13) or letters (A through L) that are randomly distributed across the page, and participants are instructed to connect the circles in alternating and ascending order (e.g., 1 to A; 2 to B). Performance is judged in terms of time to complete each trial. Time to complete Trails B (300 second maximum),

adjusted for the time taken to complete Trails A to control for sensorimotor demands of the task, is a sensitive measure of executive function and working memory.

9.1.4.5 Verbal Fluency – Category Fluency

Category fluency assesses semantic memory and language fluency in which participants name as many different exemplars of a given semantic category as rapidly as possible. Participants will be given 60 seconds to name exemplars in each of two categories: animals and vegetables.

9.1.4.6 Verbal Fluency – Phonemic Fluency

Phonemic Fluency is a measure of word generation that may be sensitive to dysfunction in the dominant frontal lobe. Participants will be given 60 seconds to name exemplars that begin with each of the two letters: F and L.

9.1.4.7 Number Span Forward and Backward

Number Span assesses two different working memory constructs: Forward Number Span measures the capacity for retaining information very briefly for the purpose of repeating it exactly, while Backward Number Span measures the ability not only to retain the information but also to mentally manipulate the numbers and recite them in reverse sequence. Numbers for both forward and backward span tests are presented with sequences ranging from 2 to 9 numbers. Two trials are administered at each sequence length. Two scores are reported for each task: number of correct trials and longest sequence repeated correctly prior to failing two consecutive trials of the same length.

9.2 Behavioral and Functional Measures

9.2.1 Clinical Dementia Rating (CDR) Scale – Sum of Boxes (SOB)

The CDR-SOB (Hughes, Berg, Danziger, Coben, & Martin, 1982) is a validated composite rating of cognition and everyday functioning used in longitudinal AD research which incorporates both informant input and direct assessment of performance. It assesses through semi structured interview 3 cognitive domains including memory, orientation, and judgement/problem solving and 3 everyday functional domains including community affairs, home and hobbies and personal care. There are 5 levels of impairment from none CDR=0 to severe CDR=3. The individual domain scores are added to create a sum of the box scores.

9.2.2 ADCS-Activities of Daily Living (ADCS-ADL) Scale

The ADCS-ADL scale is a questionnaire developed by the ADCS to assess functional performance in participants with AD (Galasko et al., 1997). Scores range from 0 to 75, with higher scores indicating better function.

9.2.3 Neuropsychiatric Inventory (NPI)

The NPI is a well-validated, reliable, multi-item instrument to assess psychopathology in AD dementia based on the results of an interview with the study partner (Cummings, 1997). The NPI evaluates both the frequency and severity of 10 neuropsychiatric features, including delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability and lability, and aberrant motor behavior, as well as evaluates sleep and appetite/eating disorders. Frequency assessments range from 1 (occasionally, less than once per week) to 4 (very frequently, once or more per day or continuously). Severity assessments range from 1 (mild) to 3 (severe). The score for each subscale is the product of severity and frequency and the total score is the sum of all subscales.

9.3 Modified Hachinski

This brief questionnaire, conducted by a clinician, incorporates information regarding medical history, cognitive symptoms and features of stroke, reported by a study partner as well as the neurological examination, and neuroimaging studies (Rosen, Terry, Fuld, Katzman, & Peck, 1980).

9.4 Sheehan Suicidality Tracking Scale (Sheehan STS)

The Sheehan STS (S-STS) is a prospective, participant self-reported or clinician administered rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors (Sheehan, Alphs, et al., 2014; Sheehan, Giddens, & Sheehan, 2014). The S-STS will be completed on a paper form at the site. At the screening visit, the recall period for completing the S-STS is 12 months prior; at all other visits, the recall period for completing the S-STS is since the last visit. Subjects who have an S-STS score > 0 should be evaluated by the investigator. If the investigator determines that a subject is at risk of suicide or self-harm, appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented. The subject must immediately be discontinued from the study. The event should be recorded as either an AE or SAE as determined by the investigator and reported within 24 hours to the Sponsor.

9.5 Research Satisfaction Survey

A Research Satisfaction Survey will be administered to the participant and study partner to evaluate satisfaction with the study. The survey may reveal specific aspects of the study that participants dislike, which can inform efforts to improve their experiences when participating in future studies. Past studies show that participant input and feedback is important for retention (Miller, Duncan, Sorrell, & Brown, 2005).

9.6 Treatment Blinding Questionnaire

Following the week 48 clinic assessment, the site Investigator and Raters will each complete a Treatment Blinding Questionnaire to document knowledge of intervention group assignment per participant.

10 EARLY DISCONTINUATION/WITHDRAWAL PROCEDURES

The entire study may be discontinued at the discretion of ADCS or Biohaven. In these circumstances the Investigator will arrange for all ongoing participants to be seen and for their study medication to be discontinued as soon as is safely possible.

Participants are free to withdraw from study participation at any time, for any reason, and without prejudice.

Discontinuation of study treatment and/or the participation of an individual participant in the study will be terminated in the following circumstances:

1. Withdrawal of informed consent by the participant or LAR. If the study partner withdraws his/her consent to participate then attempts will be made to find a replacement. In any event the participant will be continued in the study in so far as possible. Participants who withdraw consent will be advised by the Investigator regarding subsequent treatment and investigation.

2. Treatment of a participant with a non-permitted concomitant medication may necessitate discontinuation from study medications, and will be determined by the Investigator in conjunction with the Medical Monitor.

3. Adverse event or other significant medical condition which, in the opinion of the Investigator render it necessary to discontinue study medication.

4. The participant experiences a medical emergency that necessitates unblinding their treatment assignment. (See Section 6.6).

5. Any other occurrence that, in the Investigator's opinion, makes continued participation contrary to the participant's best interests.

6. Movement of participant into a long-term care nursing facility. Movement into an assisted living facility is not cause for discontinuation from the study.

Participants who discontinue active treatment for any reason will have the opportunity to continue on the protocol with further visits per protocol to the end of the double-blind phase of the study with their ongoing consent. Their continued participation will be encouraged.

The Investigators at each site will make every reasonable effort to maximize participant retention, even if the study treatment is discontinued before week 48. However, if an investigator removes a participant from study, or if a participant declines all further study participation during the study, an Early Termination Visit will be completed as close as possible to the time of study discontinuation. The Early Termination Visit may contain the same assessments as week 48, to allow collection of the main outcome measures. For further detail please refer to the Procedures Manual.

11 DEFINITION OF ADVERSE EVENTS

An adverse event (AE) or adverse experience is any untoward medical occurrence in a study participant who is administered a medicinal product, that does not necessarily have a causal relationship with the study treatment, and that occurs after informed consent is signed and up to 30 days after the study drug has been discontinued. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions, which increase in frequency or severity or worsen in nature during, or as a consequence of, use of a drug in human clinical trials, will also be considered adverse experiences. Adverse events may also include pre- or post- treatment complications that occur as a result of protocol-mandated procedures (e.g. invasive procedures such as biopsies).

An AE **does not** include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Worsening of symptoms associated with expected decline in Alzheimer's disease is not considered an adverse event in this study.
- Overdose of either study drug or concomitant medication without any signs or symptoms unless the participant is hospitalized for observation. Overdoses should be reported as outlined in Section 11.4.

A treatment emergent adverse event (TEAE) is defined as any AE that developed, worsened, or became serious after first dose of study drug and prior to 30 days after the last dose of study drug.

11.1 Evaluation and Reporting of Adverse Events

All AEs (i.e., a new event or an exacerbation of a pre-existing condition) that occur from the time informed consent is signed and up to 30 days after the study drug has been discontinued must be recorded as an AE on the AE eCRF. The Investigator must follow all AEs until the AE resolves, or until the Investigator and/or the Medical Monitor determine the event is chronic or clinically stable. If an AE remains unresolved at the conclusion of the study, the Investigator and Medical Monitor will make a clinical assessment to determine whether continued follow-up of the AE is warranted. All participants who have received at least one exposure to study therapy will be evaluated for safety of study treatment.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

11.2 Assessment of Adverse Events

All AEs must be promptly documented on the Adverse Event eCRF and assessed by the Investigator. Details of the event must include the dates of onset and resolution, severity,

relationship to study drug, seriousness, and whether the event caused the participant to withdraw from the study, outcome and timing with regard to administration of the study drug.

Severity: Severity should be graded and recorded according to the table below.

Severity	**Definition**
Mild	Awareness of event but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Inability to carry out usual activity, incapacitating, requires medical intervention

Relationship: The relationship of the Adverse Event to the study drug will be determined by the Principal Investigator, and assessed using the following definitions:

Relatedness	Description
Not Related	There is no evidence of a causal relationship and a causal relationship cannot be reasonably attributed to the study treatment or procedures. The event is clearly due to extraneous causes.
Unlikely Related	A poor temporal relationship exists between the event onset and administration of intervention. The event could easily be explained by the participant's clinical state, intercurrent illness, or concomitant therapies.
Possibly Related	A relationship cannot be ruled out with certainty and the event may be related. There is some evidence to suggest a causal relationship but the influence of other factors may have contributed to the event, such as the participant's clinical condition or concomitant treatment.
Probably Related	The event is likely related to the intervention. There is evidence to suggest a causal relationship, such as reasonable temporal sequence from treatment administration or procedure. The influence of other factors is unlikely.
Definitely Related	The event is clearly related to the intervention. There is clear evidence to suggest a causal relationship. The influence of other factors can be ruled out.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

11.3 Collection and Reporting of Serious Adverse Events

Following written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. The reporting period ends 30 days after discontinuation of dosing. In addition, the investigator should report any SAE occurring after this time period that is believed to be related to study drug or protocol-specific procedures. Serious adverse events that occur prior to initiation of study drug will be documented in the EDC as medical history, but will still need to be reported to CCI [redacted] on an SAE form as described below.

An SAE is an AE from this study that results in any of the following outcomes:

- Death
- Life-threatening situation (participant is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a participant who received study drug

- Considered significant by the investigator for any other reason

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to the study drug, but is potentially related to the conditions of the study (such as a withdrawal of previous therapy or a complication related to study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, overdose, and potential drug induced liver injury must be reported within 24 hours of the Investigator becoming aware of the event. For this study we will be capturing SAEs through both the ADCS Electronic Data Capture (EDC) system and on an SAE report form provided by CCI In addition, all applicable SAEs must be reported by the Site Investigator to the Institutional Review Board (IRB) of record according to IRB's reporting requirements for such events.

The Site Investigator is responsible for reporting all SAEs and all Other Important Medical Events to CCI via telephone, immediately or no later than 24 hours after awareness of the event. A CCI representative will then immediately notify the Biohaven Medical Monitor. An SAE form must then be submitted to CCI within 24 hours via the fax number indicated below.

CCI Safety Hotline Number for SAE telephone reports:

- North America: PPD

CCI Facsimile (fax) number for CCI SAE report forms, to be sent **within 24 hours** after awareness of the event:

- North America: PPD

The Site Investigator, or designated staff, is also responsible for entering the SAE information in the ADCS Electronic Data Capture (EDC) system (i.e., event term, start stop dates, causality, and severity) according to study-specific eCRF Completion Guidelines. The ADCS Medical Monitor and ADCS Project Director will be automatically notified via email upon entry of an SAE into the ADCS EDC system. A member of the ADCS Medical Safety team will inform the DSMB of the occurrence of any SAEs within 7 days of being reported. The DSMB may at any time request additional information from the ADCS in relation to a reported event.

If only limited information is initially available, follow-up reports are required. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent to CCI within 24 hours of the Investigator becoming aware of the updated information using the same procedure used for the transmission of the initial SAE and the same event term should be used. In addition, new or revised event information must be entered into the ADCS EDC at the same time.

All SAEs should be followed to resolution or stabilization. For any questions relating to SAEs, please contact the ADCS Medical Monitor via telephone or email at the number listed on the protocol face page.

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious adverse events that are not listed in the Investigator's Brochure as an expected AE and that the Investigator assesses as possibly related or probably related or definitely related to study drug or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs to regulatory authorities. As the clinical trial sponsor, Biohaven is responsible for, and has procedures consistent with regulations that will be followed for, expedited reporting of SUSARs.

11.4 Overdose Reporting Requirements

For the purposes of this study, an overdose is the accidental or intentional administration of any dose of study drug greater than the highest daily dose (either 140 or 280 mg as prescribed per protocol) within a calendar day. Any overdose must be reported on the eCRF. An overdose is not an AE unless it results in untoward effects. Any AEs related to the overdose must be reported on the AE and/or SAE page of the eCRF. No specific antidote for the overdose of BHV-4157 is known. Signs and symptoms of overdose should be treated according to standard of care.

11.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as AEs unless considered to be clinically significant by the site clinician. An abnormal laboratory result will be considered an AE if it is associated with clinical signs or symptoms, if the abnormality is of a degree that requires active management (e.g., discontinuation of the study drug, dose modification) or when the event is requiring treatment or other therapeutic intervention (e.g., iron supplements, blood transfusion, etc.).

The Investigator will evaluate the relationship of any significantly abnormal result to protocol treatment and clinical condition, if possible. All clinically significant abnormal laboratory results will be followed until they return to normal or become stabilized.

11.6 Pregnancy and Breast Feeding

BHV-4157 should not be used during pregnancy or while breast-feeding. The lower age limit for this study is 50 years, and women must be post-menopausal for at least 2 consecutive years or surgically sterile (bilateral tubal ligation, hysterectomy or bilateral oophorectomy) for at least 6 months prior to screening to be eligible for this study.

12 STATISTICAL METHODS

This is a multi-center double-blind placebo-controlled trial of 280 mg of BHV-4157 vs placebo taken for approximately 48 weeks with an optional 48 week open-label extension phase. There is an CCI [redacted] As the interim analysis will not stop the study for success, we have not adjusted the final analysis and have maintained the alpha at 5% in order to avoid inflating the

probability of a type 1 error. Complete details of the interim, efficacy, and safety analyses are provided in a separate Statistical Analysis Plan (SAP), which is maintained by ADCS in consultation with Biohaven.

12.1 Sample Size and Power Determination

12.1.1 Overall Study Power

Using approximately 336 randomized participants (with a 1:1 assignment 168 per arm), this study has at least 80% power to reject the null hypothesis of no efficacy in favor of the alternative that BHV-4157 is efficacious, given the assumption of a difference in the mean change from baseline to 12 months between the BHV-4157 arm and placebo arm of 2.64 points on the ADAS-Cog 11, and 0.95 points in CDR-Sum of Boxes, and under a range of effect sizes which give 93.7% probability of proceeding at the interim analysis.

This calculation assumes no more than a 26% dropout rate, which would leave 336 X 0.74 = 248 participants available at the final analysis, or 124 per arm. The calculation also assumes a standard deviation of 6 points on the change in ADAS-Cog 11 in each arm at both 6 months and 12 months, and a standard deviation of 2.3 points on the change in CDR Sum of Boxes at 12 months; in addition, a correlation of 45% between 12 month change on the co-primary ADAS-Cog 11 and CDR Sum of Boxes endpoints are assumed. These assumptions are supported by published retrospective data from historical ADCS studies (Thomas, Albert, Peterson, & Aisen, 2016). The computations use a 2-sided 2-sample t-test at 5% alpha to approximate power.

Briefly, the statistical reasoning is as follows:

1. P(pass overall) = P(pass final | pass interim)P(pass interim) $\geq$ P(pass final) P(pass interim)

2. P(pass final) = P(pass final ADAS) P(pass final CDR | pass final ADAS)

3. Numerical integration shows that P(pass final CDR | pass ADAS) is about 3% greater than P(pass final CDR), given the assumed 45% correlation between these endpoints.

Hence, if P(pass interim) = 0.937, P(pass final ADAS) = 0.92, and P(pass final CDR) =0.90, then P(pass overall) $\geq$ 0.92 x (1.03 x 0.90) x 0.937 = 0.80.

With 124 subjects per arm, the unconditional power for the ADAS-COG endpoint is 92%, if the mean difference in change is 2.64 points with standard deviation of 6 points within each arm. At this sample size, the unconditional power for the CDR-SOB endpoint is 90%, if the mean difference is 0.95 points with standard deviation of 2.3 points within each arm. Hence, if the interim analysis has power 0.937 or greater to pass, the overall power is 80% or more following the statistical reasoning given above.

For perspective, we note that the assumed difference of 2.64 points on ADAS-Cog is 68% of the decline observed in the placebo arm of 3.9 points in studies of mild to moderate AD from (Thomas,

Albert, Petersen, & Aisen, 2016). The assumed difference of 0.95 points on CDR-SOB is 59% of the decline observed in the placebo arm of 1.6 points (Thomas, Albert, Petersen, & Aisen, 2016).

12.1.2 CCI [redacted]

CCI [redacted]

12.2 Analysis Populations

Analysis populations are defined as follows:

- Enrolled Participants: Participants who signed an informed consent form and were assigned a Participant Identification number (PID).
- Randomized Participants: Enrolled participants who received a treatment assignment. This group forms the ITT population.
- Treated Participants: Enrolled and randomized participants who received at least 1 dose of blinded study therapy (BHV-4157 or placebo). This will be the primary analysis population used for safety summaries.
- The modified Intent-to-Treat (mITT) population will include all randomized participants who took at least one dose of the study medication, who have a baseline assessment of

the co-primary efficacy endpoints, and who have at least one efficacy evaluation following baseline. This will be the primary analysis population used for the efficacy analyses.

- Open-Label Extension Treated Participants: Participants enrolled in the extension phase who received at least 1 dose of open-label extension phase study therapy (BHV-4157). This will be used for safety summaries of the extension phase
- The modified Intent-to-Treat (mITT) population for the Extension Phase will include all Open-Label Extension phase participants who took at least one dose of Extension phase study medication, who have at least one efficacy evaluation during the extension phase. This will be the analysis population used for the efficacy summaries for the extension phase
- All BHV-4157 Treated Participants: Participants enrolled who received at least 1 dose of BHV-4157 in either Randomization or Extension Phase of the study. This will be used for safety summaries of the extension phase

The primary population for all efficacy analyses in the double-blind treatment phase is the mITT population, without imputation for missing values. A sensitivity uses the mITT population with multiple imputation. The Treated Participants will be used for analyses of safety endpoints.

12.3 Analysis of the Co-Primary Endpoints

The primary study hypothesis is that treatment with BHV-4157 will result in a reduction in total within-participant change from baseline on the ADAS-Cog 11 score and also on the CDR Sum of Boxes, relative to the placebo group at week 48 of the double-blind treatment phase in the mITT population. The co-primary endpoints at the final analysis will be tested using a hierarchical gatekeeper strategy: if ADAS-Cog 11 is significant at the 5% level, then CDR-SOB will also be tested at 5% significance level. If ADAS-cog is not significant at the 5% level, then CDR-SOB will not be included in the primary analysis, and will be presented for descriptive purposes only. The primary objective of the trial is met only when both coprimary endpoints are significant.

The primary analysis for each outcome uses a mixed effects repeated measures model, including all available in-clinic outcomes during the double-blind phase in the mITT population. Fixed effects in the model are APOE status (e4 carrier vs e4 noncarrier), MMSE (mild vs moderate) status, site, baseline score (ADAS-cog or CDR-SOB), treatment group (active vs placebo), visit, visit x baseline score, and visit x treatment group interaction. Visit is treated as a categorical variable. Sites with only one subject will be pooled.

A random effect will be included for participant. The within subject covariance will be unstructured. If the model fails to converge, MMSE status will be removed from the model. If the model still does not converge, the following covariance structures will be fit, sequentially, until the structure is found that results in convergence of the model: Huynh-Feldt, Toeplitz, Autoregressive (1), and Compound Symmetry. Error degrees of freedom will be calculated using Kenward-Roger approximation if an unstructured covariance structure fits appropriately; otherwise, a sandwich estimator will be utilized to estimate the covariance structure and degrees of freedom will be calculated using the between-within method (Schluter & Elashoff, 1990).

Each co-primary endpoint is tested using model-adjusted least squares means at the week 48 visit of the double-blind treatment phase. Point estimates, standard errors, 95% confidence intervals, and p-values will be presented.

Further details of the primary analysis, including sensitivity analysis and methods for handling missing data, are presented in the statistical analysis plan.

12.4 Analysis of Secondary Endpoints

If both the co-primary endpoints are significant, mean changes in the secondary endpoints from baseline to week 48 of the double-blind treatment phase are compared using the analysis strategy outlined above, or if appropriate, a two-sided, two-sample t-test. For these secondary endpoints, a Holm step-down test is conducted at 5% level to control the familywise error rate. These endpoints are: bilateral hippocampal volume as measured by volumetric MRI; NPI total scores; ADCS-ADL; and MMSE scores.

If the co-primary endpoints fail to both reach significance, then the secondary endpoints, will be analyzed as exploratory using the same strategy outlined above.

Categorical variables are summarized by treatment group using frequency distribution: number of non-missing observations and percentages will be given. Continuous variables are summarized using standard quantitative statistics: number of non-missing observations, mean, standard deviation, median and range (minimum and maximum observed values).

12.5 Analysis of Exploratory Endpoints

The exploratory endpoints include: (1) change in MoCA scores from baseline to week 48; (2) change in ADCOMS total score from baseline to week 48; (3) bilateral lateral ventricles and whole brain volume as measured by volumetric MRI; (4) a cognitive composite outcome computed using measures from the NACC Neuropsychological Test Battery (Craft Story 21 Recall (Immediate & Delayed), Benson Figure (Copy & Delayed Recall), Multilingual Naming Test (MINT), Letter & Category Fluency, Trail Making Test A & B, Number Span Forward & Backward; (5) BHV-4157 pharmacokinetics; (6) treatment response by Apo E genotype; and (7) CSF, serum and plasma biomarker panel (Aß42, Aß42/40 ratio, total tau, p-tau-181, neurogranin, NfL, YKL-40, VILIP, SNAP-25, sTREM2, GFAP) at week 24 and week 48. CSF will be assessed in a subset of the study population (estimated n=50 active, n=50 placebo). Their analyses are included in the SAP.

12.6 CCI

CCI

12.7 Open-Label Extension Phase Analysis

Any analyses of efficacy endpoints from the extension phase will be exploratory only.

12.7.1 Efficacy Analysis

Efficacy endpoints will be summarized with descriptive statistics for the Open-Label Extension Phase by treatment group and week. For the extension phase, subjects will be summarized by the original randomized treatment group and will reflect 1) continued BHV-41257 treatment and 2) Placebo subjects switched to open-label BHV-4157. Additional exploratory endpoint of evaluating long-term effects on clinical outcome measures

12.7.2 Safety Analysis

Safety endpoints include adverse events, physical exam, vital signs, health status, 12 lead ECG, laboratory determinations and participant withdrawals. Safety and tolerability data as well as demographic data will be summarized in tabular and/or graphical format for each treatment group. The incidence of all laboratory test abnormalities and the median changes from baseline will be tabulated by treatment regimen and time point. The safety population will be used for these analyses.

Safety will be presented separately for the double-blind phase and for the open-label extension phase, overall and by randomized arm.

12.7.3 Adverse Events

Treatment emergent adverse events (AE) occurring, or intensifying, after the start of study drug dosing a r e summarized descriptively for the safety population. A listing is prepared of Serious Adverse Events occurring in subjects that are enrolled but not treated. All AEs are coded

according to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables showing the number of participants and percent of unique subjects within each category are generated for each of the following types of adverse events and its relationship to study treatment (related to study treatment):

- All events
- Serious events
- Deaths
- Events leading to discontinuation of treatment
- Severe events
- Events occurring with a frequency of more than 5% in either treatment group

12.7.4 Laboratory Parameters

Laboratory parameters are summarized by visit. Frequencies of high and low values with respect to the normal range are displayed, as are shift tables comparing each treatment visit (weeks 4, 8, 12, 24, 36, and 48) and baseline visit by time point and treatment group.

12.7.5 Other Safety Parameters

Vital signs and ECG parameters are summarized across groups by visit using descriptive statistics, and at each outcome visit and at end of study.

Physical examination findings and number of participants are summarized as the count and percentage of participants by eCRF pre-defined categories at last visit. Concomitant medications are summarized by treatment group, drug class and preferred term. Vital signs are summarized by visit using descriptive statistics.

Overall interpretation results for ECGs and the Investigator interpretation results are collected as normal, abnormal not clinically significant, and abnormal clinically significant. Participants whose interpretation shifts from normal to abnormal are listed separately including description of the abnormality and any associated comments.

12.8 Randomization and Stratification

Study participants are randomly allocated in a 1:1 ratio into one of the 2 groups: treatment with 280 mg BHV-4157 or placebo. A randomization schedule will be generated and incorporated into the Electronic Data Capture system (EDC) and the randomization ID will be assigned when the site randomizes the participant. A centralized eligibility evaluation procedure will be applied for each participant. A stratified permuted block randomization procedure will be used. Screening MMSE [moderate AD: 14 to 19; mild AD: 20 to 24] and Site will be stratification factors.

12.9 Protocol Deviations, Data Blind Review, and Unblinding

Any significant event that does not comply with the inclusion/exclusion criteria, study conduct (e.g., inadequate informed consent, unreported SAEs), or study procedures (e.g., use of prohibited medications as defined by the protocol; improper breaking of the blind) will be documented as a relevant deviation.

The sponsor, or designee, will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file), which will be finalized prior to database lock. This file will include site, participant ID, deviation date, deviation type, status (major vs. minor), and a description of the protocol deviation.

Classification of deviations from the protocol as minor or major will be decided on a case-by-case basis without knowledge of the treatment assigned and before the database lock (Data Blind Review). After database lock, the responsible statistician will request the treatment codes, the study will be unblinded, and the statistical analysis will be conducted. The bioanalytical scientist, IWRS vendor, and pharmacovigilance roles may be unblinded before data are unblinded for the primary endpoint and all subjects complete the study.

13 RECORDING AND COLLECTION OF DATA

13.1 Case Report Form

The Investigator or designee will record all data collected on the electronic Case Report Form (eCRF) provided for that purpose. The site will be suitably trained on the use of the eCRF and appropriate site personnel will be provided electronic signatures.

All site entries will be made in a secured web site and the Principal Investigator will review the record for completeness. Upon completion of the review, the PI will sign electronically in the signature page of the eCRF.

The Investigator or designee will make necessary eCRF corrections. The investigator must authorize the corrections to the entered data on eCRF.

Completed eCRFs will be submitted according to the ADCS's instructions, and reviewed by the ADCS to determine their acceptability. If necessary, data correction requests will be generated for resolution by the study site.

13.2 Study Files and Participant Source Documents

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number to maintain confidentiality.

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents

include Investigators' Study Files and original participant clinical source documents generated at the study site. The term "original" means the first recording of the data.

The Investigator will ensure the site master files are maintained, including the study protocol and its amendments, IRB and regulatory approvals with associated correspondence, informed consents, study drug records, staff curriculum vitae, all correspondence, and other appropriate documents.

Participant clinical source documents may include, but are not limited to, participant hospital/clinic records, physicians' and nurses' notes, appointment books, laboratory reports, ECGs, MRI images, pathology and special assessment reports. The Investigator must assure that all original source documents are available to support monitoring activities.

13.3 Rater Training

Site staff will be trained on the assessments and certified on the study specific cognitive, functional and behavioral measures as described in Section 9. The sites will have training at the Investigator meeting and possible online training and didactic training as needed. Throughout the trial the site staff administering the assessments may have limited scales audiotaped in order to ensure ratings are being consistently administered across sites. Most scales will be collected on paper and entered via the electronic data capture system (EDC). However, some scales may be collected via an electronic capture of assessments (eCOA). Details will be provided with your rater training instructions. As the study is extended, sites must monitor their raters' certifications, and obtain re-certification before any current certifications expire.

13.4 Monitoring

During the study each site will be visited by an ADCS clinical research monitor according to the specifications in the monitoring plan for the double-blind and Open-Label Extension phases. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The Investigator will co-operate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of the monitoring visits and by prompt attention to any matters brought to his/her attention by the monitor.

13.5 Audit

ICH guidelines for GCP require independent inspection of clinical program activities. Such inspections may be performed at any time- before, during and/or after the study. The Investigator and study staff are responsible for maintaining the site master file containing all study-related regulatory documentation as outlined by ADCS Regulatory Affairs that will be suitable for inspection at any time by ADCS, Biohaven, its designees, and/or regulatory agencies. The Investigator understands and agrees to give access to the necessary documentation and files.

13.6 Retention of Data

All records connected with this clinical study will be retained for at least two years following the date of an approved marketing application [21 CFR 312.62(c)]; or at least three years from the formal discontinuation of BHV-4157 development; or seven years from the end of the study, whichever is longer. Prior to record disposal, ADCS and Biohaven may elect to extend the retention period. To ensure that these standards are applied, written permission must be granted from Biohaven before record disposal. All local laws regarding retention of records must also be followed. Study sites are required to retain all records until written notification allowing destruction is received from the ADCS.

13.7 Reporting of Study Results

Biohaven, in cooperation with ADCS, will produce an integrated Clinical Study Report, which will be submitted for approval to the Project Director and the ADCS Principal Investigator.

13.8 Quality Assurance/Quality Control

ADCS Standard Operating Procedures (SOPs) will be adhered to for all activities relevant to the quality of the study.

Documentation of all quality control procedures will be outlined in the Data Management Plan (DMP). Edit checks and listings will be run and used in conjunction with the eCRF pages to support a clinical review of the data. Documentation of all quality control procedures will be outlined in the DMP.

14 DATA SAFETY MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) will be utilized for this study. The ADCS currently has a DSMB that reviews the safety of all participants enrolled in trials on an on-going basis.

The DSMB will review the protocol, and will identify the data parameters and format of the information to be regularly reported. The DSMB will meet in person or by conference call approximately quarterly. The DSMB will typically receive reports with data by treatment group (e.g. semi-blinded group A, group B etc.) or, if requested by the DSMB, completely unblinded. The DSMB will also be informed of SUSARs as they are being reported to regulatory authorities and Investigators.

Based on the review of safety data, the DSMB will make recommendations regarding the conduct of the study to the Study Steering Committee (SSC). These may include continuing the study as designed, amending safety monitoring procedures, modifying the protocol or the informed consent form, or recommending the termination of the study.

The interim analysis will be carried out by the unblinded safety biostatistics team, and a report will be prepared for the DSMB. The DSMB will review all data pertaining to the CCI [redacted] The DSMB will then indicate whether or not the CCI [redacted] criteria have been met to the SSC that is overseeing the trial and provide its members the same data summaries for review.

For further details, please refer to the DSMB charter.

15 STUDY STEERING COMMITTEE

The SSC membership will consist of 5 members (a chairperson and advising biostatistician both independent from Biohaven and ADCS, two physician scientists from ADCS with no direct or indirect involvement in the study and one senior representative for Biohaven with no direct involvement in the ongoing management of the study. The Study Steering Committee (SSC) will receive the recommendation of the DSMB and have full access to data summaries provided to the DSMB based on the week 24 data cut. The role of the SSC is to provide clinical and scientific advice to Biohaven. The senior representative for Biohaven to the SSC will have the final responsibility for making the decision to continue or to terminate the trial. See SSC Charter for additional details.

If the CCI criteria specified in the interim analysis are not met, the SSC will remain available to receive feedback and/or non-binding recommendations from the DSMB regarding the study. If potential safety concerns arise, the SSC will advise Biohaven on whether to continue the study, consider trial modification, or consider early termination.

16 PUBLICATIONS POLICY AND SHARING OF DATA

ADCS, in collaboration with Biohaven, will publish the study results in accordance with the 2010 CONSORT guidelines (Schulz, Altman, Moher, & Group, 2010). See Appendix IV for the CONSORT Checklist and Flowchart.

As there are expected to be too few participants studied at each site for individual site's results to be statistically valid, the results of this study will be disclosed or published only in combined form based upon the statistical analysis performed by ADCS and Biohaven and will be coordinated by ADCS and Biohaven. No disclosure of study results will be permitted except as specified in a separate, written agreement between Biohaven and the Investigator. This study will be registered at www.ClinicalTrials.gov after approval of the designated IRB and prior to enrollment of the first participant, as required for publication by the International Committee of Medical Journal Editors (ICMJE).

Results will be posted on clinicaltrials.gov in accordance with requirements.

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18 APPENDICES

18.1 APPENDIX I – STUDY PLAN AND PROCEDURES AT EACH VISIT

Table 1: Schedule of Assessments and Events – Double-Blind Phase

Visit Number	1	2	3	4	5	6	7	8	9 or Early Term	10	
Study Visit Time Point	Screening (within 42 days prior to baseline)	Baseline (Week 0)	Week 2 (±3 days)	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days)	Week 24 (±7 days)	Week 36 (±7 days)	Week 48[1] (±7 days)	Follow-Up Week 52 (±7 days)	Unscheduled Visit[2]
Informed Consent	X										
Eligibility Review	X	X									
Randomization[3]		X									
Med History/Demographics	X										
Modified Hachinski Ischemic Scale	X										
Height[4] & Weight	X	X		X	X	X	X	X	X	X	
Physical Examination	X	X		X	X	X	X	X	X	X	
Neurological Examination	X										
Vital Signs[5]	X	X		X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[6]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (resting)	X					X	X		X	X	
Clinical Safety Blood Tests[7]	X	X		X	X	X	X	X[8]	X	X	
B12 (blood test)	X										
Urinalysis[9]	X	X		X		X	X		X		
HIV, HBsAg, HCV antibody	X										
ApoE4 (blood test)	X										
Blood Collection for Biomarker Banking		X					X		X		
Blood Collection for Pharmacokinetics[10]		X		X	X	X	X		X		

Visit Number	1	2	3	4	5	6	7	8	9 or Early Term	10	
Study Visit Time Point	Screening (within 42 days prior to baseline)	Baseline (Week 0)	Week 2 (±3 days)	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days)	Week 24 (±7 days)	Week 36 (±7 days)	Week 48 (±7 days)	Follow-Up week 52 (±7 days)	Unscheduled Visit
Volumetric MRI[11]	X						X		X		
Lumbar Puncture (LP)[11,12]	X						X		X		
CSF Biomarkers[13]	X						X		X		
Post-LP Safety Telephone[14]	X						X		X		
Sheehan Suicidality Tracking	X	X		X	X	X	X	X	X	X	
ADAS-Cog 11		X				X	X	X	X		
CDR-SOB		X				X	X	X	X		
NPI		X					X		X		
ADCS-ADL		X					X		X		
Craft Story 21 Recall		X							X		
Benson Complex Figure		X							X		
MINT		X							X		
Letter & Category Fluency		X							X		
Trail Making Test A & B		X							X		
Number Span Test		X							X		
MMSE	X	X					X		X		
MoCA		X					X		X		
Research Satisfaction Survey		X				X	X	X	X		
Dispense Study Drug[15]		X		X	X	X	X	X			
Study Drug Instruction Phone Call[16]			X								
Study Drug Accountability				X	X	X	X	X	X		
Treatment Blinding Questionnaire[17]									X		

1 Every effort should be made to conduct the Week 48 visit and maintain the +/- 7 day window. However, due to concerns related to the COVID-19 pandemic, the Week 48 visit window may be modified beyond the +/- 7 day window, in order to minimize any potential risks to study participant safety and to comply with governmental and local institutional guidance (e.g., study site has a policy that a clinical research visit must be delayed). Under these circumstances, the visit window may be extended (up to a maximum treatment duration of 60 weeks), but every attempt should be made to conduct the visit as close to the date the visit is due as possible. If the visit window is modified, participants should be evaluated remotely (e.g., via phone) at the time of the scheduled Week 48 visit to perform and document appropriate safety assessments. Study medication may be sent to the participant via tracked and certified courier. For any such cases, the investigator should discuss the specific circumstances of each case with the sponsor medical monitor (or designee) who must approve the request

prior to any modification of the visit window: PPD PPD Cell PPD PPD

2 The following must be collected at any unscheduled visit: vital signs, prior and concomitant medications, adverse events, and protocol deviations. All other unscheduled visit procedures are subject to PI discretion or request from the Medical Monitor.

3 Randomization must occur at the baseline visit after eligibility is confirmed.

4 Height is done at screening only.

5 Vital signs include sitting blood pressure, pulse, temperature, respiration rate, and weight.

6 The SAE reporting period starts at the screening visit (i.e., when the participant or LAR signs consent). The reporting period for non-serious AEs starts at the baseline visit at the time of receiving the first dose of study drug. The end of the reporting period for both SAEs and AEs is 30 days after the study drug has been discontinued.

7 Clinical Safety Laboratory Tests will be performed by a Central Laboratory. Assessment includes the following: Hematology (hemoglobin, hematocrit, platelets, RBC, WBC, differential count, and absolute neutrophil count), Chemistry (sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorus, bicarbonate, CPK, total protein, albumin, indirect bilirubin, direct bilirubin, total bilirubin, glucose, creatinine, BUN, uric acid, total cholesterol, LDL, HDL, triglycerides, folate).

8 Performing additional safety labs at Week 36 is now strongly encouraged, given the COVID-19 pandemic and unanticipated issues related to collecting lab samples that may potentially arise.

9 Urinalysis to include: pH, specific gravity, protein, glucose, ketones, urobilinogen, bilirubin, blood

10 A blood sample for pharmacokinetic (PK) measures in plasma should be collected at baseline, week 4, week 8, week 12, week 24, and week 48. Participants should take their dose at their routine time on the days of these visits. Date and time of last dose should be collected in case report forms for entry into the EDC system. Participants who are able scheduled for a morning visit should be instructed to hold their dose of study drug that morning until after a PK trough sample is obtained, if possible and appropriate in the judgment of the investigator. Blood samples for PK in plasma should be drawn if there are any SAEs that could possibly be drug-related or severe AEs that could be drug-related. In addition, for participants that are undergoing lumbar puncture, PK samples should be drawn at the time of lumbar puncture. Date and time of doses on the day of lumbar puncture and day prior should be collected in case report forms, for entry into the EDC system.

11 All vMRIs must be performed per imaging protocol and must use the same scanner throughout study.

- **Screening vMRI:** if a participant has **not** had an MRI performed within 6 months of screening (i.e., within 6 months from the date of informed consent), then an MRI must be performed as part of the screening requirements for this study, per the imaging protocol, and should be one of the last screening procedures performed to determine final eligibility in order to prevent participants from undergoing unnecessary MRIs. If a participant **has** had an MRI within 6 months of screening (i.e., within 6 months from the date of informed consent) **but** the MRI does not follow the study-specific imaging protocol, that MRI can be used to help determine eligibility; however, another MRI must be performed per the imaging protocol, and must occur as close to, and prior to, the baseline visit, after all other eligibility criteria have been confirmed.
- **Week 24 and week 48 vMRI:** the protocol window for vMRI at week 24 and week 48 is 14 days before and up to14 days after the clinic visit. If participant is terminating early at 36 week or after, obtain vMRI. If MRI is performed on the same day as a lumbar puncture at week 48, the vMRI must be conducted before the lumbar puncture. Otherwise, at least a 3-day window between vMRI and the lumbar puncture is required.

12 It is anticipated that lumbar puncture will be performed on an estimated 100 study participants as part of a sub-study (separate informed consent required).

13 Only for the CSF sub-study. Visit windows for CSF are: up to 14 days prior to first dose of study medication and up to 14 days prior to weeks 24 and 48. If a participant in the CSF sub-study is terminating early, they do not need to undergo lumbar puncture.

14 Post lumbar puncture safety follow up telephone call must occur 1 to 3 days after the lumbar puncture is performed.

15 First dose of study medication will be given in the clinic at the baseline clinic visit after completion of the baseline visit procedures.

16 Participants will receive a phone call during Week 2 from site study personnel in order to assess study drug tolerability. If tolerable, then the participant will be instructed to proceed with dose escalation.

17 Treatment blinding questionnaire to be administered to site PI and Raters.

Table 3: Schedule of Assessments and Events – Open-Label Extension Phase

Visit Number	1	2	3	4	5	6	7	8	9	10	
Study Visit Timepoint	Baseline[1]	Abbrev-iated Drug Dispensation Visit[2]	Ext Week 2 (+/- 7 days)	Ext Week 4 (+/- 7 days)	Ext Week 8[3] (+/- 7 days)	Ext Week 12 (+/- 7 days)	Ext Week 24 (+/- 7 days)	Ext Week 36 (+/- 7 days)	Ext Week 48 or Early Term (+/- 7 days)	Week2 Post last dose (+/- 7 days)	Unsched-uled Visit[4] (+/- 7 days)
Informed Consent	X	X									
Medical History	X										
Adverse Event Assessment	X	X	X	X	X[3]	X	X	X	X	X	X
Telephone Check-in[5] *Includes AE assessment and concomitant medication review*			X		X[3]						
Laboratory Assessments[6]	X			X	X[3]	X	X	X	X		
Urinalysis	X						X		X		
Physical Exam	X								X		
Physical Measurement - Weight	X						X		X		
Vital Signs	X	X		X		X	X	X	X	X	X
12-Lead ECG	X					X	X		X		
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X
Sheehan Suicidality Tracking Scale (S-STS)	X	X		X		X	X	X	X	X	
Dispense Study Drug	X	X		X		X	X	X			
Volumetric MRI[7]	X								X		
ADAS-Cog 11	X						X		X		
CDR-SOB	X						X		X		
Study Drug Accountability				X		X	X	X	X		
Blood Collection for Biomarker Banking							X		X		
Craft Story 21 Recall	X						X		X		
Letter & Category Fluency	X						X		X		
Number Span Test	X						X		X		
MoCA	X						X		X		

1. Baseline visit for the Extension Phase is only required if there is an extended break (≥4 weeks) in dosing between the Randomization and Extension Phases.
2. For participants who will have been off of the study drug for less than or equal to 4 weeks, the subject should come into the investigative site for an Abbreviated Drug Dispensation Visit (also "Abbreviated OLE Baseline Visit"), at which time any major medical or medications changes will be reviewed prior to dispensing riluzole. In this case, most procedures from the Week 48 visit will also serve as the Open-Label Extension Phase Baseline visit

3. Extension Week 8 is primarily to collect Liver Function tests. If a participant prefers not to come into the office, these can be collected at a local laboratory, with a telephone call confirming these were collected as well as a review of concomitant medications and an assessment of any adverse events. If the participant comes into the center, an assessment of adverse events and Liver function tests will be completed. Although all other visits can be conducted remotely as needed due to COVID-19 restrictions, under regular circumstances visits are to be completed in-person. See Protocol Section 8.1.12, Open-Label Extension Phase, for further details and requirements regarding remote visit completion due to COVID-19.
4. The following must be collected at any unscheduled visit: vital signs, prior and concomitant medications, adverse events, and protocol deviations. All other unscheduled visit procedures are subject to PI discretion or request from the Medical Monitor.
5. Telephone calls to subjects will be made between visits during Extension Phase (Weeks 2 and 8) to monitor subject condition, review concomitant medications and assess any adverse events.
6. Clinical Safety Laboratory Tests will be performed by a Central Laboratory. Assessment includes the following: Hematology (hemoglobin, hematocrit, platelets, RBC, WBC, differential count, and absolute neutrophil count), Chemistry (sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorus, bicarbonate, CPK, total protein, albumin, indirect bilirubin, direct bilirubin, total bilirubin, glucose, creatinine, BUN, uric acid, folate).
7. Volumetric MRI is not required if the participant's Double-Blind Week 48 MRI scan occurred less than than 3 months prior to their joining the Open-Label Extension Phase.

18.2 APPENDIX II - NIA/AA GUIDELINES

Criteria for all-cause dementia: Core clinical criteria

1. Interfere with the ability to function at work or at usual activities; and

2. Represent a decline from previous levels of functioning and performing; and

3. Are not explained by delirium or major psychiatric disorder;

4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

5. The cognitive or behavioral impairment involves a minimum of two of the following domains:

    a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.

    b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, and inability to plan complex or sequential activities.

    c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.

    d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.

    e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, and socially unacceptable behaviors.

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

B. Clear-cut history of worsening of cognition by report or observation; and

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:

   a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined in above section (Criteria for all-cause dementia: Core clinical criteria).

   b. Nonamnestic presentations:

      - Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
      - Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
      - Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD dementia should not be applied when there is evidence of: (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Probable AD dementia: Core clinical criteria

Meets criteria for dementia outlined above, and in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

B. Clear-cut history of worsening of cognition by report or observation; and

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:

   a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined in above section (Criteria for all-cause dementia: Core clinical criteria).

   b. Nonamnestic presentations:

      - Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.

      - Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.

      - Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD dementia should not be applied when there is evidence of: (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

18.3 APPENDIX III – CYP INHIBITORS AND INDUCERS OF INTEREST

CYP1A2 Potent and Moderate Inhibitors

Amiodarone
Artemisinin
Atazanavir
Cimetidine
Ciprofloxacin
Efavirenz
Enoxacin
Fluoroquinolones
Furafylline
Interferon
Methoxsalen
Mexiletine
Mibefradil
Tacrine
Thiabendazole
Ticlopidine
Vemurafenib
Zileuton

CYP1A2 Potent and Moderate Inducers

Barbiturates
Beta-naphthoflavone
Carbamazepine
Insulin
Methylcholanthrene
Modafinil
Nafcillin
Omeprazole
Primidone
Rifampin

Sensitive and moderately sensitive substrates of CYP2B6, CYP2C8, CYP2C9, and CYP2C19:

Enzyme	Sensitive Substrates	Moderately Sensitive Substrates
CYP2B6	bupropion	efavirenz
CYP2C8	repaglinide	montelukast, pioglitazone, rosiglitazone
CYP2C9	celecoxib	glimepiride, phenytoin, tolbutamide, warfarin
CYP2C19	S-mephenytoin, omeprazole	diazepam, lansoprazole, rabeprazole, voriconazole

18.4 APPENDIX IV – CONSORT CHECKLIST & DIAGRAM (v2010)

Section/Topic	Item No	Checklist item	Reported on page
Title and abstract			
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	

Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

CONSORT Flow Diagram (v2010)