Study Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, 76-week Study Evaluating the Safety and Efficacy of Two Doses of Simufilam in Subjects with Mild-to-Moderate Alzheimer's Disease

ClinicalTrials.gov ID: NCT05026177

Protocol Clarification Letter, dated 07-Jun-2024

Final Protocol, Version 3.0, dated 06-Feb-2023

Final Protocol, Version 2.0, dated 20-Jul-2021

Final Protocol, Version 1.0, dated 30-Jun-2021

CASSAVA sciences

MMO-125-316

To: PTI-125-06 Study file

From: [redacted] Chief Medical Officer

CC: Premier Research

Date: 07-JUN-2024

Re: Protocol Clarification for Study PTI-125-06, A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 76-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF TWO DOSES OF SIMUFILAM IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE

The purpose of this memo for Protocol **PTI-125-06, Version 3.0, February 6, 2023**, and **Version 3.0, February 20, 2023 for the Republic of Korea**, is to clarify the requirement of reporting Serious Adverse Events (SAEs) to an Institutional Review Board (IRB) or Ethics Committee (EC).

Regarding the protocol text below, the original intent was for this to refer only to SAEs/AEs for which the relevant authorities require reporting.

Protocol section 10.5 Serious Adverse Event Reporting

- "*SAEs must be immediately reported to the responsible IRB*" (Section 10.5 was intended to refer only to SAEs for which the site's relevant authorities require reporting).

Protocol section 13.5.1 Institutional Review Board

- *"The Investigator is responsible for:*
  - *Notifying the IRB within 15 calendar days of all SAEs and unexpected AEs related to study medications."* (Section 13.5.1 was intended to refer only to SAEs/AEs for which the site's relevant authorities require reporting).

Sites are to follow their IRB/EC requirements for reporting SAEs/AEs. For sites that utilize the **central WCG IRB,** they have provided the following reporting guidance:

WCG IRB Guide for Researchers, Rev 1.21:
"*Please note, only adverse events or IND safety reports that prompt a change to the protocol or consent document are required to be reported to the IRB."*

The WCG IRB based their guidance on the most current FDA recommendations which state the following:

> *"In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, only if it were unexpected, serious, and would have implications for the conduct of the study".*

FDA then described "implications" as significant changes to the protocol, monitoring requirements, informed consent, or Investigator's Brochure.

SAEs that do not meet the definition as described above are not required be immediately reported to the study Central IRB, WCG. For those SAEs that do require reporting, WCG IRB has provided the following reporting guidance:

> *"Promptly reportable information should be submitted within five (5) days of becoming aware of the event*."

If your site utilizes a local IRB/EC, and/or has site SOPs regarding the reporting of SAEs to the IRB/EC and/or other relevant authorities, please follow the relevant guidance.

Please remember:

All SAEs, regardless of IRB reportable status, are to be reported via email to Premier Pharmacovigilance within 24 hours of learning of the event, consistent with the protocol.

> **Protocol section 10.5, Serious Adverse Event Reporting:**
> *"All SAEs must be reported immediately* ***(within 24 hours of learning of the event)*** *by e-mail to:*
> *Premier Research Global Pharmacovigilance*
> [redacted]"

[redacted]

07-Jun-2024 | 12:56 CDT

[redacted]

Chief Medical Officer
Cassava Sciences, Inc.

Date

CLINICAL RESEARCH PROTOCOL

PROTOCOL PTI-125-06

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 76-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF TWO DOSES OF SIMUFILAM IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE

SPONSOR:

CASSAVA SCIENCES, INC.
6801 N. Capital of Texas Highway
Building 1, Suite 300
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Phone: 512-501-2444

This clinical study is pending support by NIH grant AG073350

Confidentiality

SUMMARY OF PROTOCOL AMENDMENT #1
(New text is underlined; omitted text is struck through)

Title page: Address is updated.
Changed: This clinical study is supported by NIH grant AG073350.
Changed to: This clinical study is pending support by NIH grant AG073350.

2.2 SAFETY PHARMACOLOGY AND TOXICOLOGY
The last sentence of the following was omitted:

"A second 6-month repeat dose oral toxicity study in rats determined the 6-month NOAEL in the rat to be < 125 mg/kg/day, based on hepatocellular vacuolation in both sexes and hepatocellular hypertrophy in females at 125 and 250 mg/kg. ~~We are evaluating whether these liver effects are rat specific.~~"

2.3 CLINICAL STUDIES
The summary of the Phase 2b study was updated to note that treatment effects were seen on plasma p-tau181 that were consistent with treatment effects on CSF biomarkers. The figure of CSF biomarker data from the phase 2b study was replaced by a figure of improvements from baseline to 6 months in 25 subjects in the 1-year open-label safety study. In the discussion of cognitive tests for the Phase 2b study, it was clarified that the episodic memory test analysis was a sensitivity analysis, effect size notation was removed from the figure, and the following clarification was **added**:

Subjects who showed no detectable simufilam in plasma or >25% noncompliance by pill counts were excluded from cognitive data (5 subjects). For the sensitivity analysis for episodic memory, the most and least impaired subjects were removed by baseline score. This sensitivity analysis removed subjects who performed so poorly they may not have understood the task and those who were at a ceiling of very few errors at baseline.

4. SUMMARY OF STUDY DESIGN

Changed: All subjects will undergo MRI during screening to ensure entry criteria are met
Changed to: Subjects will undergo MRI during screening to ensure entry criteria are met (unless recent MRI confirms entry criteria)

Clarified that ECGs are resting ECGs, and Study Day 1 is Baseline.

Clarified that participants in both PET sub-studies will be required to have an MRI during the screening period.

5.2 INCLUSION CRITERIA

 # 3. Clarified as follows: Meets National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework criteria ~~(2018)~~ for individuals in clinical Stage 4 or Stage 5 of the Alzheimer's continuum (per Table 6 in the corresponding 2018 publication[5])

#5. Clarified as follows: Evidence for AD pathophysiology, confirmed either prior to or during the screening period prior to randomization, as follows:

a. Prior to screening, confirmed with appropriate documentation by either: 1) CSF total tau/Aβ_{42} ratio (must be ≥ 0.28), or 2) an abnormal qualitative amyloid ~~or tau~~ positron emission tomography (PET) scan consistent with AD (Note – FDG PET, tau PET or amyloid SUVR values are not acceptable); or

b. During screening, subjects must demonstrate an elevated plasma P-tau181 or plasma P-tau217 level (research biomarkers that identify AD pathophysiology with high accuracy; see lab manual for details).

#12. Deleted: antidepressants

Added: Chronic medications for conditions other than AD (such as depression) must be prescribed at a stable dose for at least 4 weeks prior to screening. Medications that might have a potential confounding effect on cognitive testing (either prescription or non-prescription medications) should not be modified during the Screening Period (see Section 6.3 for additional details).

#13. Clarified that smoker means cigarette smoker.

Added: (occasional pipe or cigar smoking is permitted, but vaping is not).

#14. Clarified as follows: Availability of a person (a study partner) who~~, in the Investigator's opinion,~~ has frequent and sufficient contact with the study subject (defined as ≥10 hours per week), and can:

a. provide accurate information regarding the study subject's cognitive and functional abilities in the opinion of the Investigator,

#16. Added: Completed a COVID-19 vaccine primary series ("fully vaccinated") at least two weeks prior to Study Day 1 (randomization) or had an unambiguous COVID-19 infection diagnosed more than 3 months before the start of the screening period (to minimize or eliminate any effect on cognition that might confound a proper assessment during screening). (Note – subjects having a symptomatic COVID-19 infection [or its variants] within 3 months of the screening period should have their screening assessment delayed; vaccinated, asymptomatic subjects that test positive for COVID-19 within three months of the screening period require Medical Monitor approval to not delay screening).

5.3 EXCLUSION CRITERIA

#2. Clarified that pacemakers are excluded only if not "MRI friendly"

#4. Clarified that upper exclusion for BMI is > 37.5, not 35.0.

#7. Changed as follows: Geriatric Depression Scale (15-item) score > 8. (Note – a subject with a score > 8 may continue in screening if, in the judgment of the Investigator, the elevated score is not attributed to a major depressive episode).

#10. Clarified as follows: MRI presence of cerebral vascular pathology (including, but not limited to, intracerebral hemorrhage, infarct > 1 cm^3, > 3 lacunar infarcts, > 10 microhemorrhages, ~~multifocal or extensive~~ cortical superficial siderosis, diffuse confluent deep white matter hypertense lesions [Fazekas scale 3]), cerebral contusion, symptomatic subdural hematoma, or aneurysm.
Changed: , or space-occupying lesion deemed clinically significant in the opinion of the Investigator.
Changed to: (Note – a space-occupying lesion deemed clinically insignificant by the Investigator and confirmed by the Medical Monitor may continue screening).

#17. Added cancer exclusion: stage 0 melanoma in situ,
Added: Other potential exceptions must be discussed with the Medical Monitor.

#22. Added: Subjects with borderline hypothyroidism may be considered for rescreening after consultation with the Medical Monitor.

#25. Clarified as follows: Clinically ~~History of or current clinically~~ significant cardiac arrhythmia or heart block as evidenced by ECG in the judgment of the Investigator.

#26. Added: (Note: borderline elevations in QTcF intervals due to bundle branch block must be approved by the Medical Monitor)

#31. Added memantine: Discontinued AChEI or memantine < 12 weeks prior to randomization.

#32. Clarified as follows: Currently or previously prescribed/administered aducanumab, lecanemab or any anti-amyloid monoclonal antibody, more than two doses. ~~either currently or previously prescribed (Note – administration of aducanumab at any point during this clinical study is prohibited).~~

#33. Changed as follows: Antipsychotics (Note – low doses are allowed only if given for sleep disturbances, agitation, aggression or dementia-related psychosis, and only if the dose has been stable for at least 12 weeks prior to Study Day 1 ~~4 weeks prior to screening~~).

#34. Added SSRIs and clarified as follows: Tricyclic or SSRI antidepressants ~~and monoamine oxidase inhibitors~~ if prescribed for depression less than ~~within~~ 4 weeks prior to screening; or the

Investigator believes the dose of such medication must be modified during the Screening Period; or the Investigator believes the subject must be started on such medication during the Screening Period. Monoamine oxidase inhibitors are not permitted. ~~; all other antidepressants are allowed only if the dose has been stable for at least 4 weeks prior to screening.~~

#36. Added clarification: Use of antiepileptic medications if taken for control of seizures (Note – use of antiepileptic medications are allowed if used for mood stabilization or indications other than seizures).

#37. Added clarification: Chronic intake of opioid-containing analgesics at standard doses (use of intermittent or low-dose opioids must be approved by the Medical Monitor).

#38. Added clarification: Use of prescribed sedating H1 antihistamines (Note – fexofenadine is the preferred non-sedating antihistamine for subjects requiring such medication).

#40. Removed (re: COVID) and vaccination/exposure requirements added to inclusion criteria.

Final (now #43) added example to other: Any other medical or neurological condition (other than Alzheimer's disease), that, in the opinion of the Investigator, might represent a contributing cause to the subject's cognitive impairment, or affect cognitive assessment, subject safety, ability to comply with study assessments, drug compliance and completion of the study. This could include, for example, excessive marijuana or cannabinoid use.

6.1.2 *Storage*

Added: The Pharmacy Manual should be referenced for additional information about handling temperature excursions and record keeping requirements.

6.3 CONCOMITTANT MEDICATIONS

Clarified that "medications" are prescription medications for conditions other than AD.

Added: Medications that might have a potential confounding effect on cognitive testing, either prescription or non-prescription medications, should not be modified during the Screening Period. Medications that do not have a potential confounding effect on cognitive testing may be modified during the Screening Period if necessary, but the Investigator may wish to confer with the Medical Monitor in such a situation. After randomization to Study Drug at the Baseline Visit, the Investigator should strive to maintain concomitant medications at currently prescribed doses whenever possible. Dose modification, addition or discontinuation of medications that might have a potential confounding effect on cognitive testing (e.g., cholinesterase inhibitors and memantine) after randomization should be reviewed by the Medical Monitor.

7.1.1 *Screening visit*

Changed: Education demographic information collected changed from years to level of education.

Changed "in the 4 weeks prior to screening" to "recently" as follows:

- Review concomitant medications and any recently discontinued medications~~, in the 4 weeks prior to screening~~

Clarification in eCOA order of administration at screening as follows:

- Note: it is a study requirement to first administer the MMSE (and then the other assessments if the MMSE criterion is met)
  - MMSE
  - CDR (study partner is interviewed first in the absence of the study subject and then the subject is interviewed, by the same rater, in the absence of the study partner)

Clarified that ECG is resting ECG.

Added "or P-tau217" to lab assessments and **clarified** capture requirement of unexpected results:

- Laboratory assessments, including: routine serum chemistry, TSH, free T4, Vitamin B12 levels, HBsAg, HCV-Ab, hematology, urinalysis and urine screen for drugs of abuse. Plasma for P-tau181 or P-tau217 assessment will also be collected unless there is documented evidence of AD pathophysiology prior to screening. For subjects with diabetes, collect a blood sample for HbA1C. Unexpected, abnormal laboratory results observed during the Screening Period should be captured as Medical History and not as an AE (see Section 10.1 – Adverse Events – Definition).

Clarified that amphetamines for psychiatric symptoms acceptable if stable as follows:

- Note – amphetamines, prescribed to treat neuropsychiatric symptoms associated with progressive AD, are acceptable if prescribed for at least 12 weeks prior to the Baseline Visit (Study Day 1); the Investigator should document in the subject's file the rationale and timeframe for such use, noting that the expected positive drug screen for amphetamine does not reflect abuse of such drug.

Clarified that previous MRI results need to be approved by the Medical Monitor and that Baseline visit is Study Day 1.

- Note: previous brain MRI results, with appropriate documentation and approved by the Medical Monitor, will be accepted for up to 6 months prior

to the Baseline Visit (Study Day 1) unless a recent clinical event warrants a repeat scan.

Added:

- To remain in the study, subjects who develop COVID-19 (or its variants) or manifest a positive COVID-19 test during the screening period will need approval from the Medical Monitor.

7.1.2 *Sub-studies with PET and Fluid Biomarkers*

Clarified that PET should be scheduled after meeting other entry criteria and that PET subjects also need an MRI at screening as follows:

- Subjects participating in either amyloid or tau PET sub-studies (40 and 50 subjects/group, respectively) will be scheduled for their first PET scan prior to their Baseline Visit (Study Day 1), but after confirmation that the subject meets entry criteria based on screening procedures. They will undergo the procedure again at Week 76. Individual subjects can potentially participate in both PET imaging sub-studies, but consideration must be given to total radiation exposure based on the number of PET scans and dose each subject would receive per annum. Moreover, PET scans using different tracers must also be acquired at least 24 hours apart to ensure adequate wash-out of the previous tracer prior to new tracer administration. These subjects will also be required to undergo an MRI during the screening period to ensure their PET image data can be properly analyzed.

Clarified that PK/plasma biomarker sample collection can be done on Day 1 prior to dose:

- Subjects participating in the PET sub-studies will also have blood samples drawn for assessments of plasma-based biomarkers during the Screening Period and again at Weeks 28, 52 and 76 (270 total; 90 subjects/group). Subjects participating in the tau PET sub-study will also provide a plasma sample for PK at Weeks 28 and 76. For subjects participating in the PK and/or plasma biomarker sub-study, collection of their baseline blood samples during the Screening Period can be taken on Day 1 before administration of their first dose of Study Drug (this may help alleviate unnecessary blood sampling or having the subject return to the research center for just a blood sample).

Clarified that coagulation panel or fluoroscopy can be performed prior to LP if routine:

Subjects participating in an assessment of CSF biomarkers (90 total; 30 subjects/group) will undergo lumbar puncture prior to the Baseline Visit (Study Day 1) and again at Week 76. Research sites that routinely draw a blood sample for a "coagulation panel" prior to lumbar puncture or utilize fluoroscopy during lumbar puncture are permitted to do so.

7.1.3 *Rescreening of a Subject*

Deleted "181" from p-tau181 to capture either p-tau181 or p-tau217.

Added:

- Clinical hypothyroidism (can rescreen 3 months after being placed on supplemental thyroid replacement and manifesting a normal [or low] TSH level and a normal free T4 level)

Clarified as follows: Other reasons for screen failure will require Medical Monitor ~~Sponsor~~ approval to rescreen. Subjects undergoing rescreen, who had an inclusionary P-tau elevation and/or an acceptable screening MRI, should utilize these results during the rescreening process and not repeat these procedures.

7.1.4 Baseline Visit (Study Day 1) (Dosing Initiation)

Clarified that Study Day 1 is Baseline Visit.

Added to eCOA order of administration **(also added to 7.1.5, 7.1.6 and 7.1.7)**:

- Note: it is acceptable to simultaneously administer the study partner assessments in parallel with subject assessments (separate, qualified raters in separate rooms). When administered in parallel, the eCOA order of administration should be maintained (ADAS-cog12 and then C-SSRS for the subject; ADCS-ADL, NPI and then ZBI for the study partner).

Clarified details of ECG **(*for 7.1.4, Baseline Visit only*)**:

- A 12-lead resting ECG (5-min supine; **triplicate format**)

Clarified details of ECG ***in 7.1.5, 7.1.6 and 7.1.7 (all other Visits)***:

- A 12-lead resting ECG (5-min supine)

Added *to 7.1.7 (Week 76 / ET visit) only:*

For those 270 subjects participating in the amyloid or tau PET and Plasma Biomarker sub-studies, collect their Week 76 blood samples (including PK samples for those in the tau PET sub-study) and schedule their Week 76 scan. Investigators should attempt to schedule a second PET scan for those subjects who early terminate after 52 weeks.

7.1.8 End-of-Study / Early Termination Safety Follow-up

Added: This phone call will thus occur Week 77 to 78 for those subjects who complete all study visits, or 1 to 2 weeks after Early Termination. If the subject reports an adverse event, the subject

should be followed and treated by the Investigator until the AE has resolved or stabilized (see Section 10.1 – Adverse Events).

7.1.11 Stopping Criteria

Clarified as follows: Bodyweight loss (compared to weight at Baseline Visit [Study Day 1]) of ≥ 2 kg resulting in a BMI < 18.5 is an additional stopping criterion.

7.2.1 Clinical Laboratory Tests

Added: or P-tau217
Added: The plasma P-tau181 test is a validated assay using ADX antibodies, which shows a wide dynamic range and an AUC of 0.92 during validation without any algorithms. Validation of a P-tau217 assay is pending.

7.2.3 Preparation of Plasma Biomarker and PK Samples from PET Sub-study Participants

Changed as follows: At each blood collection for biomarkers and PK, blood samples will be drawn into two Vacutainer® tubes (10 mL per tube) containing K2EDTA. The tubes will be placed immediately on ice upon collection. Following the instructions within the Laboratory Manual, the plasma samples will be centrifuged, frozen (within 30 minutes of centrifuging), and shipped to the central laboratory. ~~Within 30 min of collection, the blood will be centrifuged at approximately 1000 X G for 15 min, preferably 4-5°C. Within 30 min of centrifuging, plasma will be transferred to polypropylene tubes and stored at -70°C until shipped to the central lab (complete instructions as per lab manual).~~

7.2.4 CSF assays

Changed as follows: Approximately 5mL of CSF will be collected and split equally into sterile polypropylene tubes. Following the instructions within the Laboratory Manual, CSF samples are to be frozen (within 30 minutes of collection) and shipped to the central laboratory. ~~CSF samples should be split, with approximately 2.5 mL shipped to the central lab (as instructed per lab manual). The remaining CSF will be retained at the study site and frozen at -70°C or below until instructions are received from the Sponsor.~~

CSF samples will be collected during the Screening Period and again at Week 76 for those subjects participating in the CSF Biomarker sub-study. We currently plan to assay the following biomarkers: ~~The biomarkers to be assayed will include:~~

- Total Tau
- P-tau181 and/or P-tau217

8.2 CLINICAL DEMENTIA RATING (CDR)

Clarified as follows: The study partner is interviewed first by a qualified rater who assesses all six domains in the absence of the study subject. The subject is then interviewed by the same rater in the absence of the study partner. ~~caregiver.~~

8.8 GERIATRIC DEPRESSION SCALE (GDS)

Added: The GDS scale score should be clinically interpreted to evaluate the potential for a major depressive episode by a clinician who has been trained on the scale and is familiar with the diagnosis of major depression.

8.9 ELECTRONIC CAPTURE OF RATING SCALES

Added: The electronic capture of the rating scales will include an audio recording for the purpose of monitoring site staff performance during scale questionnaire administration and providing constructive feedback to the raters. Subject data captured on recordings will not be analyzed as part of the trial outcomes. The Investigator or rater will read the questions out loud to study participants who will then respond. The process of questions and answers will be recorded using an audio-recording device. These highly secured recordings will not be made public at any time and will be destroyed after the Study Drug has been either approved or disapproved for use by the FDA or other pertinent regulatory bodies.

9. EARLY DISCONTINUATION

Clarified that ECG is 12-lead resting and 5 min supine.

10.1 ADVERSE EVENTS -- DEFINITION

Changed: Monitoring for AEs will start after informed consent has been obtained. ~~at dosing.~~

Added: Adverse events reported during the screening period or AEs secondary to study-related procedures should always be captured as not having a reasonable possibility the AE was caused by the Study Drug. Unexpected, abnormal laboratory results observed during the Screening Period should be captured as Medical History and not as an AE.

10.3 ADVERSE EVENTS – RELATIONSHIP TO STUDY DRUG

Changed as follows: The relationship of each AE to the Study Drug will be based on the Investigator's assessment as to whether there is a reasonable possibility the AE was caused by the Study Drug. This assessment will be based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's report, the timing of the AE in relationship to Study Drug administration/discontinuation, the Investigator's observations, and the Investigator's prior experience. The Investigator's

assessment of the relationship of the AE to the Study Drug will be recorded in the appropriate section of the EDC. ~~The relationship of each AE to the study drug will be classified into one of three defined categories as follows:~~

- ~~Unlikely – a causal relationship between the AE and the study drug is unlikely.~~
- ~~Possible – a causal relationship between the AE and the study drug is possible.~~
- ~~Probably – a causal relationship between the AE and the study drug is probably. For example, the AE is a common adverse event known to occur with the pharmacological class of the study drug; or the AE abated on study drug discontinuation and reappeared upon rechallenge with the study drug.~~

~~These three categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's report, the timing of the AE in relationship to study drug administration/discontinuation, the physician's observations and the physician's prior experience. The relationship of the AE to the study drug will be recorded in the appropriate section of the EDC.~~

11.3.3 *Other Secondary Analyses*

Clarified that p-tau181 may be p-tau181 and/or p-tau217.

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 76-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF TWO DOSES OF SIMUFILAM IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE

Approvals:

[redacted]

06-Feb-2023 | 20:37 CST

[redacted]

Date

SVP, Neuroscience
Cassava Sciences, Inc.

[redacted]

06-Feb-2023 | 17:40 CST

[redacted]

Date

Chief Med cal Officer
Cassava Sciences, Inc.

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 76-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF TWO DOSES OF SIMUFILAM IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE

Signature of Agreement for Protocol PTI-125-06

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practice (GCP) and complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR Part 312.

[redacted]

06-Feb-2023 | 15:46 PST

Coordinating Principal Investigator Signature — Date

[redacted]

Print Coordinating Principal Investigator Name

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LIST OF FIGURES

1. LIST OF ABBREVIATIONS

3xTg	triple transgenic
α7nAChR	α7 nicotinic acetylcholine receptor
$A\beta_{42}$	amyloid $beta_{1-42}$
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADME	absorption, distribution, metabolism, excretion
AE	Adverse Event
ALT	alanine transaminase
ALP	alkaline phosphatase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
BMI	Body Mass Index
BUN	blood urea nitrogen
CDR-GS	Clinical Dementia Rating – Global Score
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
CSF	cerebrospinal fluid
CSI	Cassava Sciences, Inc.
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computerized tomography
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FLNA	filamin A
GCP	good clinical practice
GDS	Geriatric Depression Scale
GGT	gamma glutamyl transpeptidase
GLP	good laboratory practice
hERG	human ether-a-go-go-related gene

iADRS	Integrated Alzheimer's Disease Rating Scale
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	insulin receptor
IRB	independent review board
ISLT	International Shopping List Test
LDH	lactose dehydrogenase
LOQ	limit of quantitation
MCI	mild cognitive impairment
MEMS	Medication Event Monitoring System
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NIA - AA	National Institute on Aging - Alzheimer's Association
NMDAR	N-methyl D-aspartate receptor
NOAEL	no observable adverse effect level
NOEL	no observable effect level
NPI	Neuropsychiatric Inventory
PAL	Paired Associate Learning
PET	positron emission tomography
PK	pharmacokinetics
PTI-125	former name of simufilam
SavaDx	blood-based diagnostic/biomarker candidate
RBC	red blood cell
SAE	serious adverse event
SOP	standard operating procedure
Tmax	time to Cmax
ULN	upper limit of normal
WBC	white blood cell
YKL40	chitinase-like protein 1, a secreted glycoprotein associated with inflammation and tissue remodeling
ZBI	Zarit Burden Interview

2. INTRODUCTION

2.1. MECHANISM OF ACTION

Cassava Sciences, Inc. is developing simufilam, a novel drug candidate designed to treat and slow the progression of Alzheimer's disease (AD). Simufilam binds with femtomolar affinity to an altered conformation of filamin A (FLNA) that is induced by beta amyloid$_{1-42}$ (Aβ_{42}), present in AD brain and critical to the toxicity of Aβ_{42}.[1-3] Simufilam binding reverses the altered FLNA conformation and restores FLNA's native shape, preventing two toxic signaling cascades of Aβ_{42}. Aβ_{42}, in monomer or small oligomer form, hijacks the α7-nicotinic acetylcholine receptor (α7nAChR) and signals via this receptor to hyperphosphorylate tau. This signaling requires the recruitment of altered FLNA to this receptor. In addition, altered FLNA also links to toll-like receptor 4 (TLR4) to allow Aβ_{42} to persistently activate this receptor, leading to inflammatory cytokine release and neuroinflammation. Normal FLNA does not associate with either α7nAChR or TLR4. In addition to disrupting the normal functions of α7nAChR and tau protein, Aβ_{42}'s toxic signaling to hyperphosphorylate tau leads to the signature tangles in AD brain. In two AD mouse models and in postmortem human AD brain tissue, simufilam restored function of three receptors that are impaired in AD: the α7nAChR, the N-methyl-D-aspartate receptor (NMDAR), and the insulin receptor (IR).[2,3] Simufilam also improved synaptic plasticity and reduced tau hyperphosphorylation, amyloid deposits, neurofibrillary tangles and inflammatory cytokine release.[2,3] We therefore expect simufilam both to improve cognition and to slow AD progression. Both mouse models used a dose of 20 mg/kg/day (equivalent to 60 mg/m^2/day).

2.2. SAFETY PHARMACOLOGY AND TOXICOLOGY

A robust nonclinical ADME, safety pharmacology, and general and genetic toxicology program has been conducted with simufilam. *In vitro* metabolic profiling showed minimal metabolism across several species including humans. Simufilam was rapidly absorbed and eliminated in *in vivo* studies in rat and dog with nearly 100% oral bioavailability, a 2.67-h half-life in dog, dose-proportional PK and no accumulation. Simufilam does not inhibit or induce major CYP450 enzymes, nor is a substrate or inhibitor of major human drug transporters at clinically relevant concentrations. Safety pharmacology studies showed no adverse effects on gross behavioral and physiological parameters in the Irwin test of CNS toxicity in rats, no adverse effects on respiratory rate, tidal volume or minute volume in the rat respiratory test, and no adverse effects on arterial blood pressure, heart rate and ECG parameters in the dog cardiovascular study. The *in vitro* hERG test for cardiotoxicity also indicated no adverse effect. A full battery of genotoxicity studies was conducted (*in vitro* bacterial Ames, *in vitro* chromosomal aberration, and *in vivo* rat micronucleus test) and all were negative. An *in vitro* specificity screen showed no significant activation or inhibition

of a panel of 68 receptors, channels, and transporters.

Simufilam was tested in single dose and repeat dose oral toxicity studies of up to 6 months in rats and 9 months in dogs. A 6-month repeat dose oral toxicity study in rats (PTI-125-NC-049) used the same doses as a 28-day study (50, 500 and 1000 mg/kg/day), which found 500 mg/kg/day to be the no-adverse-effect-level (NOAEL). In the 6-month study, the toxicological response was characterized by decreased body weights and adverse structural and functional alterations in the liver of 500 and 1000 mg/kg/day animals, including increased hepatic weight, hepatocellular hypertrophy and vacuolation, single/multiple basophilic/ eosinophilic/clear cell focus, hepatocellular degeneration, pigmentation, and oval cell hyperplasia. The presence of bile pigment was consistent with cholestasis. These findings correlated with changes to the clinical chemistry profile, including increased ALP and total/direct bilirubin. Over the 1-month recovery period, there was complete recovery of the hepatocellular degeneration and partial recovery of hepatocellular hypertrophy; other microscopic findings in the liver remained. The NOAEL in this 6-month study was 50 mg/kg/day (equivalent to 300 mg/m^2), corresponding to a safety margin of 6- and 1.6-fold based on C_{max} and AUC over the 100 mg b.i.d. dose in human subjects. A second 6-month repeat dose oral toxicity study in rats determined the 6-month NOAEL in the rat to be < 125 mg/kg/day, based on hepatocellular vacuolation in both sexes and hepatocellular hypertrophy in females at 125 and 250 mg/kg.

In a 9-month toxicity study in dogs (PTI-125-NC-050), the no-effect-level (NOEL) of simufilam was 25 mg/kg. The high dose of 200 mg/kg/day was decreased to 150 mg/kg/day after 1 month due to bodyweight loss considered unsustainable for 9 months. Clinical signs were slight hypoactivity and incidences of slight muscle fasciculations early in the study, and salivation. There were no pathology findings, but the high dose was considered adverse due to two unexplained deaths. The 75 mg/kg/day NOAEL (equivalent to 1500 mg/m^2) provides 38- and 19-fold safety margins based on C_{max} and AUC over the 100 mg b.i.d. dose in subjects.

Simufilam showed no mutagenic or clastogenic responses in a standard battery of genotoxicity assays.

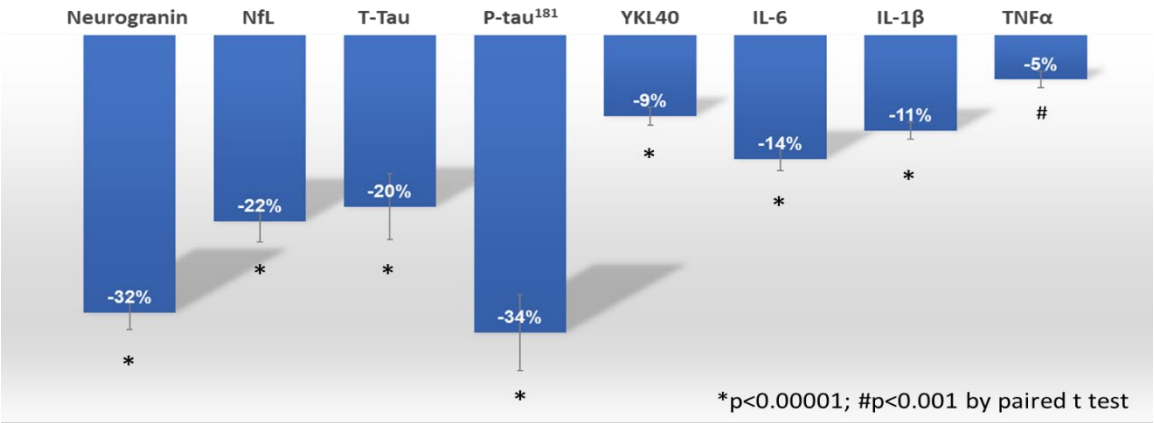
2.3. CLINICAL STUDIES

A first-in-human, double-blind, single ascending dose clinical study (PTI-125-01) was conducted in healthy normal volunteers, age 18-45 with oral dosing solution. Doses were placebo, 50, 100 and 200 mg (equivalent to 31, 62, and 123 mg/m^2, respectively) administered to three different groups of volunteers. The study showed dose proportional PK, a half-life ranging from 4.5 to 6 h, and there were no drug-related adverse events (AEs).

In a 28-day phase 2a study (PTI-125-03), 13 subjects with mild-to-moderate AD received

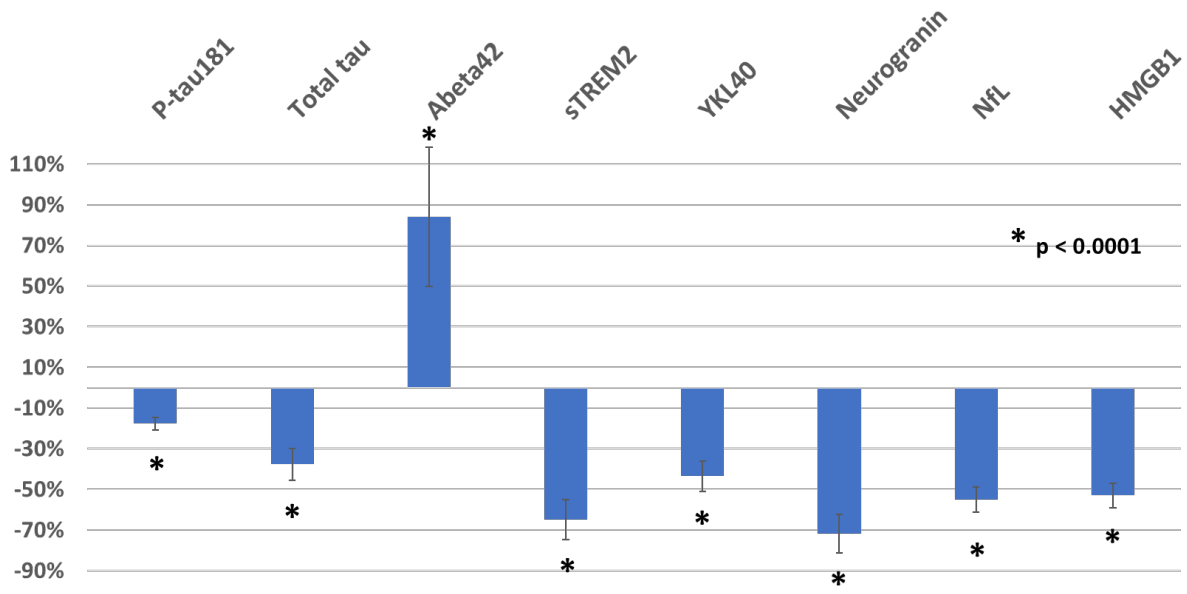
simufilam 100 mg b.i.d. as oral tablets. Subjects had Mini-Mental State Exam (MMSE) scores ≥ 16 and ≤ 24 and were age 50-85 with a CSF total tau/$A\beta_{42}$ ratio ≥ 0.30. A second CSF sample was collected on Day 28, allowing assessment of change from baseline in biomarkers using commercial ELISA kits. All 8 biomarkers that are elevated in AD were significantly reduced from baseline (**Fig. 1**).[4] $A\beta_{42}$, which is low in AD, was increased slightly but non-significantly. Reduced inflammatory cytokines and YKL-40 indicated reduced neuroinflammation. A reduced neurodegenerative drive was suggested by reductions in neurogranin, neurofilament light chain, and total tau. The robust reduction in phospho-tau (P-tau181) confirms the mechanism of action of simufilam. Simufilam was safe and well tolerated in all subjects.

Figure 1. Phase 2a Mean Change from Baseline to Day 28 in CSF biomarkers (±SEM)



A phase 2b randomized, placebo-controlled clinical study (PTI-125-02) of simufilam 50 or 100 mg tablets or placebo (1:1:1) enrolled 64 mild-to-moderate AD subjects with MMSE 16-26. CSF biomarker analyses were conducted blind to treatment and timepoint by an outside lab, and screening and Day 28 samples for each subject were measured in triplicate in the same ELISA plates. Albumin and immunoglobulin G (IgG) were measured by immunoblotting and quantified by densitometric quantitation. Plasma p-tau181, measured by Quanterix Corporation using their Simoa platform, was significantly reduced versus placebo. The treatment effect on plasma p-tau181 was consistent with treatment effects in CSF biomarkers, suggesting disease modification and replicating Phase 2a results in a well-controlled study. An open-label safety study of simufilam 100 mg showed larger improvements from baseline at 6 months (n=25) (**Fig. 2**).

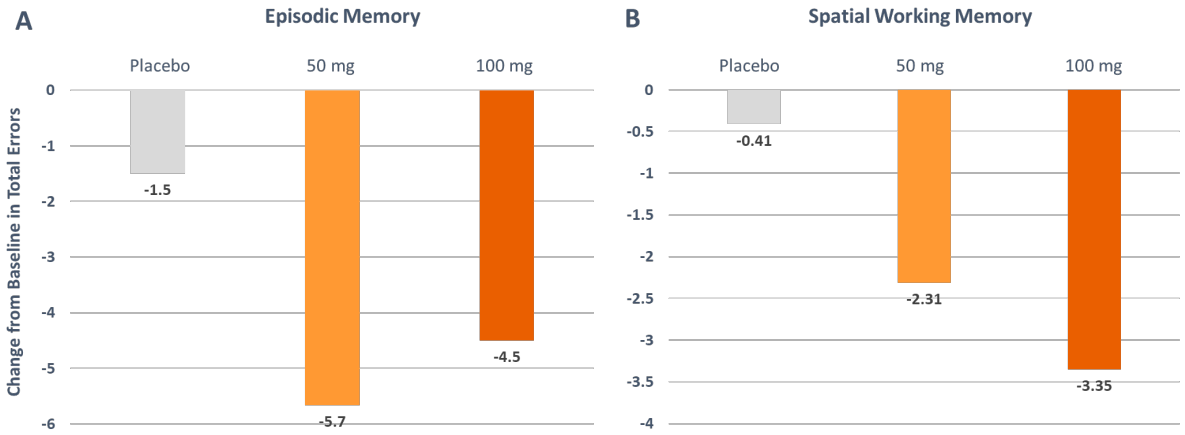
Figure 2. Percent Change from Baseline in CSF Biomarkers at 6 Months (±SD)



The secondary endpoints in the Phase 2b study were two cognitive measures using the Cambridge Neuropsychological Test Automated Battery. Subjects were assessed on the Paired Associate Learning (PAL) test, measuring episodic memory, and a test of spatial working memory. The primary outcome measure for each was total errors, with errors imputed for more difficult levels not reached in the PAL test. Simufilam produced encouraging mean improvements from baseline in spatial working memory and in a sensitivity analysis for episodic memory for both doses, suggesting cognitive enhancement (**Fig. 3**). Without the sensitivity analysis, the PAL test did not show a clear treatment effect. Subjects who showed no detectable simufilam in plasma or >25% noncompliance by pill counts were excluded from both cognitive tests (5 subjects). For the sensitivity analysis for episodic memory, the most and least impaired subjects were removed by baseline score. This sensitivity analysis removed subjects who performed so poorly they may not have understood the task and those who were at a ceiling of very few errors at baseline. Cognitive enhancement by simufilam is supported by preclinical data showing improved function of α7nAChR, NMDAR and insulin receptors and improved synaptic plasticity in 3xTg AD mice and in postmortem human AD brain tissue.

In both Phase 2 clinical studies, simufilam was well tolerated and no subjects discontinued due to AEs.

Figure 3. Phase 2b Mean Change from Baseline to Day 28 in Total Errors in Memory Test



3. STUDY OBJECTIVES

The primary objective of this study is to investigate the safety and efficacy of simufilam in slowing cognitive and functional decline following 76-week, repeat-dose oral administration in mild-to-moderate AD subjects, 50-87 years of age. Secondary objectives are to assess neuropsychiatric symptoms and to replicate the CSF biomarker effects observed in the two Phase 2 studies (PTI-125-03 and PTI-125-02) after 76 weeks of simufilam treatment. A third objective is to investigate the effect of simufilam treatment on plasma biomarkers as well as anatomical correlates of disease progression (brain volume [hippocampus, ventricles and whole brain]; amyloid and tau deposition in the brain).

4. SUMMARY OF STUDY DESIGN

In this Phase 3 clinical study, approximately 1,083 subjects with mild-to-moderate AD (361 per arm) will receive placebo or 50 mg tablets of simufilam or 100 mg tablets of simufilam, twice daily, for 76 weeks. Randomization (1:1:1) will be stratified by low or high MMSE (16-20 and 21-27).

Subjects, 50-87 years of age, will be selected for screening based on a diagnosis of AD consistent with Stages 4 or 5 on the Alzheimer's continuum (National Institute on Aging – Alzheimer's Association 2018[5]). Subjects must have MMSE $\geq$ 16 and $\leq$ 27, and a Clinical Dementia Rating Global Score (CDR-GS) of 0.5, 1 or 2. Finally, subjects must have confirmed PET or fluid biomarker evidence of AD pathophysiology prior to randomization (see Section 5.2 – Inclusion Criteria for details).

Once subjects have been satisfactorily screened for study participation, visits to the research clinic will occur on Study Day 1 and at Weeks 4, 16, 28, 40, 52, 64 and 76.

The co-primary endpoints include the 12-item Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog12) and the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), both assessed as the change from baseline to the end of the double-blind treatment period (Week 76).

Secondary endpoints include the integrated Alzheimer's Disease Rating Scale (iADRS), Neuropsychiatric Inventory (NPI), MMSE, and Clinical Dementia Rating Sum of Boxes (CDR-SB). A brief questionnaire assessing caregiver burden, the Zarit Burden Interview (ZBI), will be collected as an additional secondary endpoint.

Safety will be evaluated by adverse event monitoring, vital signs, clinical labs, and the Columbia Suicide Severity Rating Scale (C-SSRS) at every visit. Subjects will undergo MRI during screening to ensure entry criteria are met (unless recent MRI confirms entry criteria); however, 150 subjects (50 subjects per treatment group) will also undergo repeat MRI assessments at Weeks 40 and 76 to assess both long-term safety and drug impact on brain volume as noted above. Resting ECGs will be conducted at Baseline (Study Day 1) and Weeks 4, 40 and 76. A complete physical and neurological examination will be performed at screening, and brief examinations will be performed at all other visits. Weight will be measured during the Screening Period, at Baseline (Study Day 1) and at all other visits.

A limited number of research sites will be invited to participate in one or more sub-studies to assess the impact of simufilam on anatomical and biomarker endpoints, including: change from baseline in CSF biomarkers (30 subjects/group), brain volume via MRI (50 subjects/group), and amyloid and tau PET (40 and 50 subjects/group, respectively). Participants in both PET sub-studies will be required to have an MRI during the screening period and provide plasma for a biomarker sub-study. Participants in the tau PET sub-study will also provide additional plasma for a PK exposure-response analysis. Changes from baseline for these imaging and fluid biomarkers represent additional secondary endpoints.

The ninety subjects (30 per group) in the CSF sub-study will undergo lumbar puncture during the Screening Period and again at the Week 76 End-of-Treatment Visit to collect CSF biomarkers.

An independent Data Safety Monitoring Board (DSMB) will meet periodically to review subject safety assessments and determine if dosing may continue. A charter will be developed with specific guidance for the DSMB.

5. SUBJECT SELECTION

5.1. STUDY POPULATION

Approximately 1,083 subjects will be enrolled in the study.

5.2. INCLUSION CRITERIA

Each subject must meet the following Inclusion Criteria:

1. Capable of providing either written informed consent or, if incapable of written consent, permission to participate can be obtained from a legally authorized representative. Verbal assent to the study procedures and schedule is required of all participants. Genotyping for apolipoprotein E (ApoE) will be included in the informed consent, and participants must consent to this to be included in the study. If, in the Investigator's judgment, a subject loses capacity to consent during the duration of the study, a legally authorized representative must consent on behalf of the subject. All consent processes must be undertaken prior to any study procedures.

2. Age ≥ 50 and ≤ 87 years at the time of the informed consent, male or female.

3. Meets National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework criteria for individuals in clinical Stage 4 or Stage 5 of the Alzheimer's continuum (per Table 6 in the corresponding 2018 publication[5]).

4. The subject and/or study partner report a gradual and progressive change in memory for ≥ 6 months.

5. Evidence for AD pathophysiology, confirmed either prior to or during the screening period prior to randomization, as follows:

    a. Prior to screening, confirmed with appropriate documentation by either: 1) CSF total tau/$A\beta_{42}$ ratio (must be ≥ 0.28), or 2) an abnormal qualitative amyloid positron emission tomography (PET) scan consistent with AD (Note – FDG PET, tau PET or amyloid SUVR values are not acceptable); or

    b. During screening, subjects must demonstrate an elevated plasma P-tau181 or plasma P-tau217 level (research biomarkers that identify AD pathophysiology with high accuracy; see lab manual for details).

6. MMSE score ≥ 16 and ≤ 27 at screening.

7. CDR-GS must be 0.5, 1 or 2.

8. If female, either surgically sterile or postmenopausal for at least 1 year.

9. Male subjects must be willing to use contraception during the study. With female partners of childbearing potential, male subjects, regardless of their fertility status, must agree to either remain abstinent or use condoms in combination with one additional highly effective method of contraception (e.g., oral or implanted contraceptives, or intrauterine devices) or an effective method of contraception (e.g., diaphragms with spermicide or cervical sponges) during the study and for 14 days after Study Drug dosing has been completed.

10. Fluency in a language of the research site and the utilized assessment materials.

11. Has adequate visual and auditory acuity (in the Investigator's judgment) that is sufficient to complete all scheduled assessments (eyeglasses and hearing aids are permitted).

12. If receiving background AD medications, including cholinesterase inhibitors, memantine, neuroleptics, anxiolytics, or sleep medications, the dosing regimen must be stable for at least 12 weeks prior to Study Day 1 (randomization) and should be expected to remain stable during the study (Note – barbiturates, meprobamate, and high dose benzodiazepines are not allowed, while low dose benzodiazepines, zolpidem, zaleplon and suvorexant are permitted). Chronic medications for conditions other than AD (such as depression) must be prescribed at a stable dose for at least 4 weeks prior to screening. Medications that might have a potential confounding effect on cognitive testing (either prescription or non-prescription medications) should not be modified during the Screening Period (see Section 6.3 for additional details).

13. The subject has not been a cigarette smoker or chewed tobacco for at least 3 years (occasional pipe or cigar smoking is permitted, but vaping is not).

14. Availability of a person (a study partner) who has frequent and sufficient contact with the study subject (defined as ≥10 hours per week), and can:

    a. provide accurate information regarding the study subject's cognitive and functional abilities in the opinion of the Investigator,

    b. agree to comply with and participate at all scheduled visits and study procedures,

    c. sign the necessary consent form,

    d. maintain the same level of interaction with the study subject throughout the study duration.

15. Individuals who have participated in a clinical study with an investigational drug

targeting the underlying AD process are permitted to participate in this study on a case-by-case basis after consultation between the Principal Investigator and the Sponsor. Subjects known to have been randomized to placebo do not require such consultation and are permitted to participate.

16. Completed a COVID-19 vaccine primary series ("fully vaccinated") at least two weeks prior to Study Day 1 (randomization) or had an unambiguous COVID-19 infection diagnosed more than 3 months before the start of the screening period (to minimize or eliminate any effect on cognition that might confound a proper assessment during screening). (Note – subjects having a symptomatic COVID-19 infection [or its variants] within 3 months of the screening period should have their screening assessment delayed; vaccinated, asymptomatic subjects that test positive for COVID-19 within three months of the screening period require Medical Monitor approval to not delay screening).

5.3. EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

1. Residence in a skilled nursing facility requiring 24-hour care (Note – subjects may reside in an assisted living facility if they do not need 24-hour care).

2. Any contraindications to study procedures (e.g., potential subjects with a pacemaker that is not "MRI friendly").

3. A medical condition or treatment with an anticoagulant that would interfere with a lumbar puncture for those subjects being considered for participation in the CSF biomarker assessment.

4. BMI < 18.5 or > 37.5

5. Evidence of a neurologic condition other than AD that, in the judgment of the Investigator, significantly contributes to the subject's dementia, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, Huntington's disease, or normal pressure hydrocephalus.

6. Subjects with any current primary psychiatric diagnosis other than AD if, in the judgment of the Investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the subject's ability either to comply with study procedures or to complete the study. Patients with a history of schizophrenia or chronic psychosis are excluded.

7. Geriatric Depression Scale (15-item) score > 8. (Note – a subject with a score > 8 may continue in screening if, in the judgment of the Investigator, the elevated score is not attributed to a major depressive episode).

8. Affirms suicidal ideation in response to questions number 4 or 5 in the C-SSRS during the past 3 months (i.e., "active suicidal ideation with some intent to act, without specific plan," or "active suicidal ideation with specific plan and intent") or affirms any of the questions contained in the Suicidal Behavior section of the C-SSRS as applicable during the past 12 months.

9. Meets DSM-V criteria for alcohol or substance use disorder within 2 years before the Screening Period.

10. MRI presence of cerebral vascular pathology (including, but not limited to, intracerebral hemorrhage, infarct > 1 cm^3, > 3 lacunar infarcts, > 10 microhemorrhages, cortical superficial siderosis, diffuse confluent deep white matter hypertense lesions [Fazekas scale 3]), cerebral contusion, symptomatic subdural hematoma, or aneurysm. (Note – a space-occupying lesion deemed clinically insignificant by the Investigator and confirmed by the Medical Monitor may continue screening).

11. History of transient ischemic attack (TIA) or stroke within 12 months of screening, or history of a stroke concurrent with the onset of dementia.

12. History of seizure within 12 months of screening.

13. History of severe head trauma; history of head trauma with loss of consciousness > 10 min within 12 months of screening; history of head trauma concurrent with the onset of dementia; history of head trauma likely to be contributing to the subject's cognitive impairment in the Investigator's judgment.

14. Onset of dementia secondary to cardiac arrest, surgery with general anesthesia, or resuscitation.

15. Clinically significant, untreated or inadequately treated sleep apnea that is likely to be contributing to the subject's cognitive impairment in the Investigator's judgment.

16. Insufficiently controlled diabetes mellitus, defined as:

    a. requiring insulin treatment (unless subject has been stable for at least 4 weeks prior to screening on a once-daily dose of long-acting insulin), or

    b. HbA1C > 8.0% during the Screening Period.

17. Malignant tumor within 3 years before screening (except definitively treated squamous

or basal cell carcinoma, stage 0 melanoma in situ, cervical carcinoma in situ, localized non-progressive prostate cancer, localized stage 1 bladder cancer or colon polyp resolved by excision, per judgment of the Investigator). Other potential exceptions must be discussed with the Medical Monitor.

18. Known positive HIV status.

19. Positive HBsAg or HCV-Ab during screen.

20. Positive urine drug screen for substances of abuse.

21. Vitamin B12 level lower than the normal limit at the time of screening (and that remains below on repeat testing). Subjects may be enrolled following initiation of B12 therapy for at least 4 weeks prior to randomization with confirmation of a normal level upon repeat testing.

22. Thyroid-stimulating hormone (TSH) levels greater than the upper limit of normal and a free thyroxine (free T4) lower than the lower limit of normal; subjects on thyroid supplementation for hypothyroidism must be on a stable dose for ≥ 3 months before screening. Subjects with borderline hypothyroidism may be considered for rescreening after consultation with the Medical Monitor.

23. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – subjects with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN).

24. History or diagnosis of clinically significant ischemic heart disease (e.g., myocardial infarction or unstable angina within 1 year of screening), moderate to severe congestive heart failure, cardiomyopathy, myocarditis or valvular heart disease of clinical significance in the Investigator's judgment.

25. Clinically significant cardiac arrhythmia or heart block as evidenced by ECG in the judgment of the Investigator.

26. Clinically significant abnormality on screening electrocardiogram (ECG), including, but not necessarily limited to, a confirmed QT interval by the Fridericia correction formula (QTcF) > 470 msec (females) or > 450 msec (males) based on WHO 2016 guidelines. (Note: borderline elevations in QTcF intervals due to bundle branch block must be approved by the Medical Monitor)

27. Insufficiently controlled hypertension (defined, at rest, as systolic BP > 170 mmHg or diastolic BP > 100 mmHg; if an initial BP reading is elevated, an additional

measurement during the Screening Period could be used before excluding a potential subject for insufficiently controlled hypertension).

28. Hypotension (systolic BP < 90 mmHg) or bradycardia with a heart rate less than 50 beats per minute during screening (out of range values may be repeated once for confirmation).

29. Use of medications that in the Investigator's opinion will contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or other study procedures.

30. Donepezil > 10 mg/day, currently or within 12 weeks of Study Day 1 (randomization).

31. Discontinued AChEI or memantine < 12 weeks prior to randomization.

32. Currently or previously prescribed/administered aducanumab, lecanemab or any anti-amyloid monoclonal antibody, more than two doses.

33. Antipsychotics (Note – low doses are allowed only if given for sleep disturbances, agitation, aggression or dementia-related psychosis, and only if the dose has been stable for at least 12 weeks prior to Study Day 1).

34. Tricyclic or SSRI antidepressants if prescribed for depression less than 4 weeks prior to screening; or the Investigator believes the dose of such medication must be modified during the Screening Period; or the Investigator believes the subject must be started on such medication during the Screening Period. Monoamine oxidase inhibitors are not permitted.

35. Immunosuppressants, including systemic corticosteroids, if taken in clinically immunosuppressive doses (steroid use for allergy or inflammation is permitted).

36. Use of antiepileptic medications if taken for control of seizures (Note – use of antiepileptic medications are allowed if used for mood stabilization or indications other than seizures).

37. Chronic intake of opioid-containing analgesics at standard doses (use of intermittent or low-dose opioids must be approved by the Medical Monitor).

38. Use of prescribed sedating H1 antihistamines (Note – fexofenadine is the preferred non-sedating antihistamine for subjects requiring such medication).

39. Use of nicotine therapy (all dosage forms including a patch), varenicline (Chantix), or similar therapeutic agent within 4 weeks prior to screening.

40. Loss of a significant volume of blood (> 450 mL) within 4 weeks of randomization.

41. Clinically significant abnormalities on screening laboratory tests in the judgment of the Investigator.

42. Unstable medical condition that is clinically significant in the judgment of the Investigator, including significant neurologic, hepatic, renal, endocrinologic, cardiovascular, gastrointestinal, pulmonary, hematologic, immunologic or metabolic disease.

43. Any other medical or neurological condition (other than Alzheimer's disease), that, in the opinion of the Investigator, might represent a contributing cause to the subject's cognitive impairment, or affect cognitive assessment, subject safety, ability to comply with study assessments, drug compliance and completion of the study. This could include, for example, excessive marijuana or cannabinoid use.

6. STUDY DRUG

6.1. SIMUFILAM PHYSICAL DESCRIPTION AND PREPARATION

Investigational simufilam and matching placebo will be supplied by Cassava as coated tablets including 50 and 100 milligram active strengths.

All remaining unused Study Drug will be returned to the Sponsor or designee.

6.1.1 Packaging and Labeling

Simufilam or placebo tablets in plastic bottles will be supplied in 70-count bottles for a 4-week supply or 188-count bottles for a 12-week supply. Bottles include a desiccant canister and are closed with a foil seal and child-resistant (CR) cap. Each bottle contains 7 or 10 days of extra medication to accommodate scheduling flexibility with clinic visits.

A Medication Event Monitoring System (MEMS®) that is 21 CFR Part 11 compliant will be used to track adherence to the b.i.d. dosing schedule. MEMS® caps will be supplied to replace the conventional CR cap on each bottle. One (1) MEMS® cap will be assigned to each subject for use throughout the study. Each MEMS® cap has an LCD display that provides immediate visual indication of the number of doses taken that day and the number of hours since the prior dose that day, resetting to zero each night. Instructions on management and use of MEMS® caps will be provided in the Pharmacy manual and during site training.

Each bottle is labeled with a unique double-blind ID number that is randomly assigned to a treatment. A computer-based clinical study management system will specify the bottle ID number to be dispensed according to the subject's treatment randomization.

6.1.2 Storage

The investigational drug supplies must be stored in a locked cabinet or room with limited access at controlled room temperature, 20-25º C (68-77º F) and protected from moisture. The Pharmacy Manual should be referenced for additional information about handling temperature excursions and record keeping requirements.

6.1.3 Drug Accountability

The Investigator will be responsible for monitoring the receipt, storage, dispensing and accounting of all study medications according to site standard operating procedures (SOPs). All records documenting the chain of custody for the study medication must be retained in the site study file. Accurate, original site records must be maintained of drug inventory and dispensing. All records must be made available to the Sponsor (or designee) and appropriate regulatory agencies upon request.

6.2. ADMINISTRATION AND DOSING REGIMEN

Subjects will be randomized to receive placebo, or 50 mg or 100 mg simufilam b.i.d. (approximately 361 subjects per treatment group). Study Drug can be taken with or without food.

6.3. CONCOMITANT MEDICATIONS

Use of prescription or non-prescription medications will be recorded during the study. Chronic prescription medications for conditions other than AD must be stable for at least 4 weeks prior to screening. Medications that might have a potential confounding effect on cognitive testing, either prescription or non-prescription medications, should not be modified during the Screening Period. Medications that do not have a potential confounding effect on cognitive testing may be modified during the Screening Period if necessary, but the Investigator may wish to confer with the Medical Monitor in such a situation. After randomization to Study Drug at the Baseline Visit, the Investigator should strive to maintain concomitant medications at currently prescribed doses whenever possible. Dose modification, addition or discontinuation of medications that might have a potential confounding effect on cognitive testing (e.g., cholinesterase inhibitors and memantine) after randomization should be reviewed by the Medical Monitor. [Note – see Inclusion Criterion #12 and Exclusion Criteria #30 and #31 for additional details regarding background medications frequently prescribed to patients with AD].

7. STUDY PROCEDURES

Appendix A presents the Schedule of Activities.

Prior to any study-related activities, the Informed Consent Form (ICF) must be signed and dated by the subject (or a legally authorized representative) and the study partner. The format and content of the ICF must be agreed upon by the Principal Investigator(s), the appropriate IRB and the Sponsor. The signed and dated ICF must be retained by the Investigator in the subject's file.

7.1. EVALUATIONS BY VISIT

Follow-up visits can be scheduled ± five (5) days from the targeted Study Visit date.

7.1.1. Screening Period (No greater than a 60-day duration prior to Study Day 1)

The Sponsor recognizes the Screening Period assessments and procedures may not necessarily be completed in a single visit. A subject is permitted to be screened over more than one calendar day if, in the Investigator's judgment, such scheduling will optimize the accuracy of Screening Period assessments and procedures. The following will be completed during the Screening Period:

- Informed Consent.
- Review of Inclusion and Exclusion Criteria
- Collect demographic information (e.g., sex, date of birth, race/ethnicity, level of education)
- Medical and surgical history
- Review concomitant medications and any recently discontinued medications
- To the extent such information is available, review and record any investigational drugs administered during past clinical study participation regardless of the date of such participation
- History of drug, alcohol and tobacco use
- eCOA order of administration at screening
    - Note: it is a study requirement to first administer the MMSE (and then the other assessments if the MMSE criterion is met)
        - MMSE

- CDR (study partner is interviewed first in the absence of the study subject and then the subject is interviewed, by the same rater, in the absence of the study partner)
- Geriatric Depression Scale
- C-SSRS – Baseline/screening version

- Complete physical and neurologic examination; including measurement of key vital signs (blood pressure [supine], temperature, pulse rate), height and weight (to calculate BMI)
- A 12-lead resting ECG (5-min supine)
- Laboratory assessments, including routine serum chemistry, TSH, free T4, Vitamin B12 levels, HBsAg, HCV-Ab, hematology, urinalysis and urine screen for drugs of abuse. Plasma for P-tau181 or P-tau217 assessment will also be collected unless there is documented evidence of AD pathophysiology prior to screening. For subjects with diabetes, collect a blood sample for HbA1C. Unexpected, abnormal laboratory results observed during the Screening Period should be captured as Medical History and not as an AE (see Section 10.1 – Adverse Events – Definition).
  - Note – amphetamines, prescribed to treat neuropsychiatric symptoms associated with progressive AD, are acceptable if prescribed for at least 12 weeks prior to the Baseline Visit (Study Day 1); the Investigator should document in the subject's file the rationale and timeframe for such use, noting that the expected positive drug screen for amphetamine does not reflect abuse of such drug.
- Once the clinical and laboratory assessments above have been completed and verified to be consistent with study participation, schedule brain MRI to confirm subject meets MRI-specific entry criteria
  - Note: previous brain MRI results, with appropriate documentation and approved by the Medical Monitor, will be accepted for up to 6 months prior to the Baseline Visit (Study Day 1) unless a recent clinical event warrants a repeat scan.
  - Subjects participating in the MRI sub-study assessment of brain volume (150 total; 50 subjects/group), including the hippocampus, ventricles, and whole brain, will have, in addition to the MRI during the Screening Period, subsequent MRI scans at Weeks 40 and 76.
- To remain in the study, subjects who develop COVID-19 (or its variants) or

manifest a positive COVID-19 test during the screening period will need approval from the Medical Monitor.

7.1.2. Sub-studies with PET and Fluid Biomarkers

Selected research sites will participate in additional sub-study assessments to determine the effect of simufilam on anatomical and biomarker secondary endpoints.

- Subjects participating in either amyloid or tau PET sub-studies (40 and 50 subjects/group, respectively) will be scheduled for their first PET scan prior to their Baseline Visit (Study Day 1), but after confirmation that the subject meets entry criteria based on screening procedures. They will undergo the procedure again at Week 76. Individual subjects can potentially participate in both PET imaging sub-studies, but consideration must be given to total radiation exposure based on the number of PET scans and dose each subject would receive per annum. Moreover, PET scans using different tracers must also be acquired at least 24 hours apart to ensure adequate wash-out of the previous tracer prior to new tracer administration. These subjects will also be required to undergo an MRI during the screening period to ensure their PET image data can be properly analyzed.
- Subjects participating in the PET sub-studies will also have blood samples drawn for assessments of plasma-based biomarkers during the Screening Period and again at Weeks 28, 52 and 76 (270 total; 90 subjects/group). Subjects participating in the tau PET sub-study will also provide a plasma sample for PK at Weeks 28 and 76. For subjects participating in the PK and/or plasma biomarker sub-study, collection of their baseline blood samples during the Screening Period can be taken on Day 1 before administration of their first dose of Study Drug (this may help alleviate unnecessary blood sampling or having the subject return to the research center for just a blood sample).
- Subjects participating in an assessment of CSF biomarkers (90 total; 30 subjects/group) will undergo lumbar puncture prior to the Baseline Visit (Study Day 1) and again at Week 76. Research sites that routinely draw a blood sample for a "coagulation panel" prior to lumbar puncture or utilize fluoroscopy during lumbar puncture are permitted to do so.

7.1.3. Rescreening of a Subject

Individuals who have given informed consent and fail to meet the Inclusion and/or Exclusion criteria (screen failure) may not be rescreened if the screen failure is due to non-

eligible MMSE (<16), MRI or P-tau results. If screen failure occurs for the following reasons, the subject is allowed to rescreen once:

- Low vitamin B12 requiring supplemental therapy (can retest after 4 weeks)
- MMSE of 28 (can rescreen after 8 weeks)
- Clinical hypothyroidism (can rescreen 3 months after being placed on supplemental thyroid replacement and manifesting a normal [or low] TSH level and a normal free T4 level)

Other reasons for screen failure will require Medical Monitor approval to rescreen. Subjects undergoing rescreen, who had an inclusionary P-tau elevation and/or an acceptable screening MRI, should utilize these results during the rescreening process and not repeat these procedures.

7.1.4. Baseline Visit (Study Day 1) (Dosing Initiation)

Subjects will come to the clinic in the morning. Prior to dosing, the following assessments will be conducted:

- Confirmation of Inclusion/Exclusion criteria
- Confirm subject has been fully vaccinated for COVID-19 for at least two weeks if there is no history of a prior COVID-19 infection
- Review of concomitant medications
- Adverse event monitoring
- Vital signs (blood pressure [supine], temperature, pulse).
- Weight
- Brief physical and neurologic examination
- Note: the brief physical and neurologic examination performed on Study Day 1 and at all subsequent visits will include an assessment of the following: general appearance; cardiovascular, pulmonary, and abdominal examination, as well as an examination of any other system in response to subject-reported symptoms; cranial nerves [II-XII], tone, power, deep tendon reflexes, coordination, and gait.
- eCOA order of administration

- Note: it is acceptable to simultaneously administer the study partner assessments in parallel with subject assessments (separate, qualified raters in separate rooms). When administered in parallel, the eCOA order of administration should be maintained (ADAS-cog12 and then C-SSRS for the subject; ADCS-ADL, NPI and then ZBI for the study partner).
  - ADAS-Cog12
  - ADCS-ADL
  - NPI
  - ZBI
  - C-SSRS – Since Last Visit version

- A 12-lead resting ECG (5-min supine; triplicate format)
- Clinical laboratory tests (blood and urine)
- Genotyping for ApoE

Once all Baseline Visit (Study Day 1) procedures and assessments have been completed, the subject is randomized to a treatment and the bottle of Study Drug to be dispensed is assigned by the computer-based study management system. A Medication Event Monitoring System (MEMS®) cap is drawn from stock for permanent assignment to the subject and initialized via the computer interface. Before removing Study Drug from the bottle, remove the original closure and apply the MEMS® cap as a replacement. Just prior to administering the first dose of Study Drug, remove the MEMS® cap and remove one (1) tablet.

Subjects will be administered Study Drug at least 1 hour before leaving the clinic. The subject will be discharged with their supply of Study Drug. The study partner will be trained on the features and proper use of the MEMS® cap and instructed to administer Study Drug twice daily with or without food. The study partner should be advised that a dose can be up to 4 hours late, but, if a dose is missed, the next dose should NOT be doubled.

Information and instruction for the computer-based study management system, and the MEMS® cap will be covered during site training, and written reference information will be included in the Pharmacy Manual.

For all follow-up visits, subjects will be instructed to bring their Study Drug bottle to the clinic. At each visit, the MEMS® cap will be read into the computer-based study management system to inform the site about the subject's Study Drug adherence. The

MEMS® cap will be removed from the returned bottle and applied to the newly dispensed bottle of Study Drug.

7.1.5. Weeks 4, 16, 40 and 64 Follow-up Visits

Subjects will return to clinic for these scheduled visits within a ± 5-day "window."

- Vital signs (blood pressure [supine], temperature and pulse)
- Weight
- Brief physical and neurologic examination
- Adverse event monitoring
- Use of concomitant medications
- eCOA order of administration
    - Note: it is acceptable to simultaneously administer the study partner assessments in parallel with subject assessments (separate, qualified raters in separate rooms). When administered in parallel, the eCOA order of administration should be maintained (ADAS-cog12 and then C-SSRS for the subject; ADCS-ADL and then ZBI for the study partner).
        - ADAS-Cog12 (whenever possible, within 1 hour of the time of day administered at the Baseline Visit (Study Day 1), and by the same rater)
        - ADCS-ADL
        - ZBI
        - C-SSRS – Since Last Visit version
- Clinical laboratory tests (blood and urine)
- Weeks 4 and 40 only: 12-lead resting ECG (5 min supine)
- Week 40 only: for those 150 subjects participating in the MRI sub-study to determine the effect of simufilam on brain volume, schedule their Week 40 scan.

7.1.6. Weeks 28 and 52 Follow-up Visits

Subjects will return to clinic for these scheduled visits within a ± 5-day "window." On the Week 28 Visit, subjects in the tau PET sub-study should come to the clinic before taking their a.m. dose and have their PK blood sample collected prior to their dose.

- Vital signs (blood pressure [supine], temperature and pulse)
- Weight
- Brief physical and neurologic examination
- Adverse event monitoring
- Use of concomitant medications
- eCOA order of administration
    - Note: it is acceptable to simultaneously administer the study partner assessments in parallel with subject assessments (separate, qualified raters in separate rooms). When administered in parallel, the eCOA order of administration should be maintained (ADAS-cog12, MMSE and then C-SSRS for the subject; ADCS-ADL, NPI and then ZBI for the study partner).
        - ADAS-Cog12 (whenever possible, within 1 h of the time of day administered at the Baseline Visit (Study Day 1), and by the same rater)
        - ADCS-ADL
        - MMSE
        - NPI
        - ZBI
        - C-SSRS – Since Last Visit version
- Clinical laboratory tests (blood and urine)
- For those 270 subjects participating in the amyloid or tau PET and Plasma Biomarker sub-studies, collect their Week 28 and Week 52 blood samples (including PK at Week 28 for those in the tau PET sub-study)

7.1.7. Week 76 End-of-Treatment Visit / Early Termination (ET) Visit

Subjects will return to clinic for this scheduled visit within a ± 5-day "window." Subjects in the tau PET sub-study should **not** take an a.m. (morning) dose of Study Drug prior to their blood draw.

- Vital signs (blood pressure [supine], temperature and pulse)
- Weight
- Brief physical and neurologic examination

- Adverse Event monitoring
- Use of concomitant medications
- eCOA order of administration
    - Note: it is acceptable to simultaneously administer the study partner assessments in parallel with subject assessments (separate, qualified raters in separate rooms except for CDR). When administered in parallel, the eCOA order of administration should be maintained (ADAS-cog12 and then MMSE for the subject, and ADCS-ADL, for the study partner; for the CDR, the study partner is interviewed first in the absence of the study subject and then the subject is interviewed, by the same rater, in the absence of the study partner; the C-SSRS is then administered to the subject, and the NPI and ZBI are then administered to the study partner).
        - ADAS-Cog12 (whenever possible, within 1 hour of the time of day administered at the Baseline Visit (Study Day 1), and by the same rater)
        - ADCS-ADL
        - MMSE
        - CDR
        - NPI
        - ZBI
        - C-SSRS – Since Last Visit version
- A 12-lead resting ECG (5 min supine)
- Clinical laboratory tests (blood and urine)
- For those 270 subjects participating in the amyloid or tau PET and Plasma Biomarker sub-studies, collect their Week 76 blood samples (including PK samples for those in the tau PET sub-study) and schedule their Week 76 scan. Investigators should attempt to schedule a second PET scan for those subjects who early terminate after 52 weeks.
- For those 150 subjects participating in the MRI sub-study to determine the effect of Study Drug on brain volume, schedule their Week 76 scan.

- For those 90 subjects participating in the CSF Biomarker sub-study, perform a lumbar puncture to collect CSF (5 mL) after all other testing has been completed.

Note: Early Termination subjects do not need to complete the eCOA if performed within 30 days of the ET Visit (see Section 9 – Early Discontinuation)

7.1.8. End-of-Study / Early Termination Safety Follow-up

The subject and/or study partner will receive a follow-up phone call 7-14 days after the last dose of Study Drug for adverse event monitoring. If needed, a follow-up clinic visit will be scheduled. This phone call will thus occur Week 77 to 78 for those subjects who complete all study visits, or 1 to 2 weeks after Early Termination. If the subject reports an adverse event, the subject should be followed and treated by the Investigator until the AE has resolved or stabilized (see Section 10.1 – Adverse Events).

7.1.9. Treatment after Study Completion

The Sponsor plans to initiate an open-label extension study for subjects who have completed participation in Study PTI-125-06. Should a subject elect to participate in the open-label extension study, the End-of-Study Follow-up (Section 7.1.8) will not be conducted.

7.1.10. Unscheduled Visits and Discontinuation due to AEs

For unscheduled visits due to AEs, any assessments conducted will be at the discretion of the Investigator and pertinent to the AE. If a decision is made to discontinue the subject from Study Drug, the Sponsor will be notified immediately. The subject should be followed and treated by the Investigator until the AE has resolved or stabilized (see Section 10.1 – Adverse Events). Restarting the subject on Study Drug will be a mutual decision by the Investigator and the Sponsor. See also Section 9.0 – Early Discontinuation.

7.1.11. Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to ensure subject safety and to evaluate liver event etiology during administration of Study Drug. Potential discontinuation of Study Drug for abnormal liver function tests should be considered by the Investigator in consultation with the designated medical monitor if the study subject meets one or more of the following criteria:

- ALT or AST ≥ 4x ULN;
- ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN;
- ALT or AST ≥ 3x ULN if associated with the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash

and/or eosinophilia; or

- ALP elevations, if deemed of liver origin and drug-related as follows:
  - ALP > 3x ULN;
  - ALP > 2.5x ULN and total bilirubin > 2x ULN; or
  - ALP > 2.5x ULN if associated with the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia.

In the event of discontinuation due to abnormal liver function tests, the subject will be appropriately investigated to determine the potential cause and referred to a physician experienced in the treatment of hepatic disorders.

Study Drug should be discontinued if a subject: (1) positively affirms suicidal ideation in response to questions number 4 or 5 in the Suicidal Ideation section of the C-SSRS, or (2) reports any suicidal behavior or non-suicidal self-injurious behavior since their last visit in response to the C-SSRS Suicidal Behavior questions. The subject should be referred to a psychiatrist or an appropriate health care professional for further evaluation and management.

Bodyweight loss (compared to weight at Baseline Visit [Study Day 1]) of ≥ 2 kg resulting in a BMI < 18.5 is an additional stopping criterion.

7.2. LABORATORY ASSESSMENTS

7.2.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed during the Screening Period, Baseline (Study Day 1) pre-dose, and at all follow-up visits:

- Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count.

- Serum Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphate, blood urea nitrogen (BUN), total bilirubin, creatinine, albumin, globulin, total protein, uric acid, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), lactose dehydrogenase (LDH).

- Urinalysis: color, specific gravity, pH, protein, glucose, ketones, occult blood, nitrites and leukocyte esterase. A "reflex" microscopic examination will be performed if protein, occult blood, nitrites or leukocyte esterase is present on the basic analysis.

- Screening Period: During the Screening Period only, bloods will be drawn for TSH, free T4, Vitamin B12, HepBsAg, HCV-Ab, HbA1C (diabetic subjects only) and plasma P-tau181 or P-tau217 (Note – plasma collection for P-tau181 or P-tau217 is not required if subject has documented evidence of AD pathophysiology prior to screening). The plasma P-tau181 test is a validated assay using ADX antibodies, which shows a wide dynamic range and an AUC of 0.92 during validation without any algorithms. Validation of a P-tau217 assay is pending. Urine to screen for drugs of abuse (amphetamines, cocaine, opiates and phencyclidine) will also be collected during the Screening Period.

7.2.2. Collection of Whole Blood Samples for ApoE Genotyping

Whole blood samples for genotyping ApoE will be collected at the Baseline Visit (Study Day 1) (please review instructions as per the Lab Manual).

7.2.3. Preparation of Plasma Biomarker and PK Samples from PET Sub-study Participants

At each blood collection for biomarkers and PK, blood samples will be drawn into two Vacutainer® tubes (10 mL per tube) containing K2EDTA. The tubes will be placed immediately on ice upon collection. Following the instructions within the Laboratory Manual, the plasma samples will be centrifuged, frozen (within 30 minutes of centrifuging), and shipped to the central laboratory.

7.2.4. CSF Assays

Approximately 5mL of CSF will be collected and split equally into sterile polypropylene tubes. Following the instructions within the Laboratory Manual, CSF samples are to be frozen (within 30 minutes of collection) and shipped to the central laboratory.

CSF samples will be collected during the Screening Period and again at Week 76 for those subjects participating in the CSF Biomarker sub-study. We currently plan to assay the following biomarkers:

- Total Tau
- P-tau181 and/or P-tau217
- Neurogranin
- sTREM2
- Amyloid-beta 42
- Neurofilament light chain

8. COGNITIVE AND FUNCTIONAL ASSESSMENTS

8.1. MINI-MENTAL STATE EXAM (MMSE)

The MMSE[6] is a set of standardized questions covering several target areas: orientation, registration, attention and calculation, short-term verbal recall, naming, repetition, 3-step command, reading, writing, and visuospatial cognitive assessment. Administration of the MMSE is estimated to take approximately 10 minutes.

8.2. CLINICAL DEMENTIA RATING (CDR)

Washington University's CDR[7] characterizes six domains of cognitive and functional performance applicable to AD and related dementias: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The study partner is interviewed first by a qualified rater who assesses all six domains in the absence of the study subject. The subject is then interviewed by the same rater in the absence of the study partner. A CDR global score can be calculated by accessing Washington University's online algorithm (https://biostat.wustl.edu/~adrc/cdrpgm/index.html) where 0 = no dementia, and scores of 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively. The sum of boxes (i.e., CDR-SB)[8] can also be calculated by summing the six individual domain scores. This detailed quantitative general index may provide more information than the CDR-GS in patients with mild dementia.

8.3. ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE SUBSCALE 12 (ADAS-COG12)

The ADAS-Cog[9,10] is a psychometrician-administered battery comprised of several cognitive domains including memory, comprehension, praxis, orientation, and spontaneous speech. The ADAS-Cog12 (which includes Delayed Word Recall) will be administered to all subjects at various key visits throughout the study.

8.4. NEUROPSYCHIATRIC INVENTORY (NPI)

A study partner interview, the 12-item NPI[11] records frequency and severity of common neuropsychiatric symptoms in dementia (Hallucinations, Delusions, Agitation/aggression, Dysphoria/depression, Anxiety, Irritability, Disinhibition, Euphoria, Apathy, Aberrant motor behavior, Sleep and nighttime behavior change, Appetite and eating change). The study partner is then asked to rate their own distress for the subject's behavioral symptoms occurring in the past 4 weeks.

8.5. ALZHEIMER'S DISEASE COOPERATIVE STUDY – ACTIVITIES OF DAILY LIVING (ADCS-ADL-AD)

The ADCS-ADL[12] is a 23-item study partner questionnaire that covers both basic activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal).

8.6. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

The C-SSRS[13] is an assessment tool used to assess the lifetime suicidality of a subject (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit).

8.7. ZARIT BURDEN INTERVIEW (ZBI)

The ZBI[14,15] is a 22-item scale designed to assess the stress or burden experienced by caregivers of people with dementia. The ZBI will be administered as an interview with the caregiver. The scale consists of 22 statements reflecting how people can feel when taking care of another person. The statements are phrased as questions for the caregiver to indicate how often they feel the way described in the statement. The 5 possible responses for each item are Never, Rarely, Sometimes, Quite Frequently, and Nearly Always.

8.8. GERIATRIC DEPRESSION SCALE (GDS)

The GDS[16] is a 30-item yes/no question test designed to screen for depression in elderly persons. The GDS short form (15-items)[17] version utilized in this study will be clinician administered with caregiver input. Subjects will be evaluated for symptoms of depression during the Screening Period. The GDS scale score should be clinically interpreted to evaluate the potential for a major depressive episode by a clinician who has been trained on the scale and is familiar with the diagnosis of major depression.

8.9. ELECTRONIC CAPTURE OF RATING SCALES

The assessments MMSE, CDR, ADAS-Cog12, GDS, NPI, ADCS-ADL, C-SSRS, and ZBI will be captured electronically by an eCOA platform that is 21 CFR Part 11 compliant. Data collected by eCOA will be transferred directly to the EDC vendor's database.

The electronic capture of the rating scales will include an audio recording for the purpose of monitoring site staff performance during scale questionnaire administration and providing constructive feedback to the raters. Subject data captured on recordings will not be analyzed as part of the trial outcomes. The Investigator or rater will read the questions out loud to study participants who will then respond. The process of questions and answers will be recorded using an audio-recording device. These highly secured recordings will not

be made public at any time and will be destroyed after the Study Drug has been either approved or disapproved for use by the FDA or other pertinent regulatory bodies.

9. EARLY DISCONTINUATION

Subjects may choose to discontinue Study Drug or study participation at any time, for any reason, and without prejudice. Moreover, a subject may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral or administrative reasons. Discontinued subjects should be followed according to medical practice standards, and the outcome documented. Follow-up is required if the subject is discontinued due to an adverse event (AE). Any comments (spontaneous or elicited) or complaints made by the subject and the reason for termination and the date of stopping the drug must be recorded in the Case Report Form (CRF) and source documents.

The following must be completed and documented in the source documents and CRFs for all subjects who discontinue the study early:

- The reason for early study discontinuation. If the subject is withdrawn for more than one reason, each reason should be documented in the source documents and the most clinically relevant reason should be entered on the CRF.
- Vital signs (blood pressure, temperature and pulse), brief physical and neurologic examination, weight, clinical laboratory tests, 12-lead resting ECG (5 min supine), use of concomitant medications and adverse events should be obtained at discharge prior to release.
- Blood draw for plasma biomarkers
- ADAS-Cog12, MMSE, CDR, ADCS-ADL, NPI, ZBI and C-SSRS (as detailed in Section 7.1.7 – Early Termination Visit), if not performed within the last 30 days.

10. ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

10.1. ADVERSE EVENTS – DEFINITION

An Adverse Event (AE) is any undesirable event that occurs to a subject during a study, whether or not that event is considered related to Study Drug. Monitoring for AEs will start after informed consent has been obtained. Examples include:

- Any treatment-emergent signs and symptoms (events that are marked by a change from the subject's baseline/entry status [e.g., an increase in severity or frequency of pre-existing abnormality or disorder])
- All reactions from Study Drug, an overdose, abuse of drug, withdrawal phenomena, sensitivity or toxicity to Study Drug
- Apparently unrelated illnesses
- Injury or accidents (Note: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate medical events [e.g., for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately])
- Extensions or exacerbations of symptoms, subjective subject-reported events, new clinically significant abnormalities in clinical laboratory, physiological testing or physical examination

All AEs, whether or not related to Study Drug, must be fully documented on the AE page of the CRF and in the subject's clinical chart. Adverse events reported during the screening period or AEs secondary to study-related procedures should always be captured as not having a reasonable possibility the AE was caused by the Study Drug. Unexpected, abnormal laboratory results observed during the Screening Period should be captured as Medical History and not as an AE.

In the event that a subject is withdrawn from the study because of an AE, it must be recorded on the CRF as such. The subject should be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

The Investigator must report all directly observed AEs and all spontaneously reported AEs. The Investigator will ask the subject a non-specific question (e.g., "Have you noticed anything different since your dose of the study medication?") to assess whether any AEs have been experienced since the last assessment. AEs will be identified and documented in the Electronic Data Capture (EDC) system in appropriate medical terminology. The severity and the relationship to the Study Drug will be determined and reported in EDC (see below).

10.2. ADVERSE EVENTS – SEVERITY RATING

The severity of each AE should be characterized and then classified into one of three clearly defined categories as follows:

- Mild – the AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.
- Moderate – the AE produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment.
- Severe – the AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

These three categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's report and the physician's observations. The severity of the AE should be recorded in the appropriate section of the EDC.

10.3. Adverse Events – Relationship to Study Drug

The relationship of each AE to the Study Drug will be based on the Investigator's assessment as to whether there is a reasonable possibility the AE was caused by the Study Drug. This assessment will be based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's report, the timing of the AE in relationship to Study Drug administration/discontinuation, the Investigator's observations, and the Investigator's prior experience. The Investigator's assessment of the relationship of the AE to the Study Drug will be recorded in the appropriate section of the EDC.''''

10.4. Serious Adverse Events and Unexpected Adverse Events – Definitions

A Serious Adverse Event (SAE) includes (but is not limited to) an experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (i.e., the subject is at immediate risk of death from the reaction as it occurs). "Life-threatening" does not include an event that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
- In-patient hospitalization (hospital admission, not an emergency room visit) or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity (i.e., a substantial disruption of the subject's ability to carry out normal life functions).

- A congenital anomaly/birth defect.

In addition, medical and scientific judgment should be exercised in deciding whether other situations should be considered an SAE (i.e., important medical events that may not be immediately life-threatening or result in death but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above). Examples of such medical events include (but are not limited to): allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

An **unexpected** AE is one for which the specificity or severity is not consistent with the current Investigator's Brochure. For example, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure listed only elevated hepatic enzymes or hepatitis.

Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

10.5. SERIOUS ADVERSE EVENTS REPORTING

The reporting of SAEs by the Sponsor to regulatory authorities (e.g., FDA) is a regulatory requirement. Each regulatory agency has established a timetable for reporting SAEs based upon established criteria. Likewise, it is the responsibility of the Principal Investigator to report SAEs to the IRB.

All SAEs must be reported immediately **(within 24 hours of learning of the event)** by e-mail to:

Premier Research Global Pharmacovigilance
[redacted]

Do not delay reporting a suspected SAE to obtain additional information. Any additional information, if collected, can be reported to the Sponsor as a follow-up to the initial report.

SAEs must be immediately reported to the responsible IRB.

In the case of a death or other SAE that has occurred within 30 days after receiving Study Drug, the Principal Investigator must also report such an event within 24 hours of being notified. Your local IRB may also require these reports.

In the event of any SAE (other than death), the subject will be instructed to contact the

study physician (Principal Investigator or designee) using the phone number provided in the Informed Consent Form. All subjects experiencing an SAE will be seen by a Principal Investigator or designee as soon as feasible following the report of an SAE.

11. STATISTICAL CONSIDERATIONS

11.1. RANDOMIZATION

Randomized treatments will be assigned by subject numbers in a randomly generated numeric sequence.

The randomization code will not be revealed to study subjects, Investigators, clinical staff, study monitors or the Sponsor until all subjects have completed therapy and the database has been finalized and locked.

Under normal circumstances, the blind should not be broken. The blind may be broken only if specific emergency treatment is indicated. The date, time, and reason for the unblinding must be documented in the CRFs, and the Medical Monitor must be informed as soon as possible.

11.2. ANALYSIS POPULATIONS

The Intent-To-Treat (ITT) analysis set includes all randomized subjects. All efficacy analyses will be conducted in this analysis set and subjects will be included in the group to which they were randomized.

The Safety analysis set includes all subjects who receive study treatment. All Safety analyses will be completed in the Safety analysis set and subjects will be included in the group based on the treatment actually received.

11.3. STATISTICAL ANALYSIS

11.3.1. Primary Efficacy Analysis

Each of the two co-primary endpoints will be analyzed using a linear mixed model for repeated measurements. The dependent variable is the change from baseline and the model will include fixed effects for treatment group (three levels), week (7 levels, corresponding to Weeks 4, 16, 28, 40, 52, 64 and 76), the treatment group-by-week interaction, and the randomization stratification variable. The baseline value of the corresponding endpoint will be included as a covariate and the unstructured covariance model will be used. The Baseline Visit (Study Day 1) ADAS-Cog12 and ADCS-ADL assessments will represent the baseline value for these variables.

For each of the two co-primary endpoints, the primary analysis will compare the 100 mg group and the placebo group at Week 76 using a two-sided test at the alpha = 0.05 level of significance. Study success requires that both co-primary comparisons are statistically significant.

11.3.2 Key Secondary Analysis

If both primary comparisons are statistically significant, then the corresponding comparisons at Week 76 for the 50 mg group versus the placebo group will be tested at the alpha = 0.05 level of significance (two-sided).

11.3.3 Other Secondary Analyses

The iADRS[18,19] is a linear combination of scores from two well-established, widely accepted, therapeutically sensitive measures of AD: the ADAS-Cog and ADCS-iADL (the instrumental component of the ADCS-ADL). The iADRS has been validated and statistical properties of the composite performance have been described[20]. All items of the ADAS-Cog12 and the ADCS-iADL will be included to generate this primary efficacy composite measurement without additional weighting.

Secondary clinical endpoint data (iADRS, NPI, MMSE, and ZBI) measured repeatedly will be analyzed by linear mixed models for repeated measurements, as described above for the primary analysis.

Plasma assays may include P-tau181 and/or P-tau217, SavaDx, neurofilament light chain, and other biomarkers. All plasma biomarker data and MRI data measured repeatedly will be analyzed by linear mixed models for repeated measurements, as described above for the primary analysis.

CSF biomarker endpoints to be analyzed currently include: 1) neurogranin, 2) neurofilament light chain, 3) total tau, 4) P-tau181 and/or P-tau217, 5) sTREM2, and 6) $A\beta_{42}$. Additional CSF biomarkers may be measured. All CSF biomarker data, PET imaging data, and CDR-SB will be analyzed using ANCOVA models with treatment group as a factor and the baseline value of the corresponding endpoint as a covariate.

All secondary analyses will be conducted using two-sided tests at the alpha = 0.05 level of significance, with no adjustments for multiplicity.

11.4. SAFETY ANALYSIS

Adverse events reported on case report forms will be mapped to preferred terms and organ systems using the MedDRA mapping system. Vital signs and clinical laboratory results will be descriptively summarized in terms of change from screening values.

11.5. SAMPLE SIZE

Approximately 1,083 subjects will be enrolled in this study. The sample size was determined by a power analysis of ADAS-Cog in a similar population over 76 weeks. This analysis determined that the comparison between an active arm and placebo requires group sizes of 289 to provide 90% power to detect a 45% difference from placebo at 76 weeks, based on the use of a two-sided test at the alpha = 0.05 significance level. The power calculation assumes a true mean change from baseline for placebo of 6.0 points and a standard deviation of 10.0 points. Assuming a drop-out of 20%, each treatment group should enroll 361 subjects.

12. STUDY TERMINATION

The study will be terminated following completion of the study or at any time at the discretion of the Sponsor.

13. DATA COLLECTION, RETENTION, AND MONITORING

13.1. CASE REPORT FORMS

The CRF will be provided as an Electronic Data Capture (EDC) system that will serve as the collection method for subject data. The subjects in the study will not be identified by name on any study documents to be collected by the Sponsor (or CRO designee) but will be identified by a unique subject number.

All clinical information requested in this protocol will be recorded in the EDC system. It is strongly recommended that data entry be completed within 48 hours of a subject's visit. In case of error noted on paper source documents, the correction will be noted, initialed, and dated.

EDC data must be reviewed and verified for accuracy and signed-off by the staff personnel before database lock. Paper source documents, if used, will remain at the Investigator's site at the completion of the study.

13.2. AVAILABILITY AND RETENTION OF INVESTIGATIONAL RECORDS

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee) and Regulatory Agency (e.g., FDA) inspectors upon request. To assure accuracy of data collected in the EDC, it is mandatory that Sponsor representatives have access to original source documents (e.g., subject records, subject charts, and laboratory reports). During review of these documents, the subject's anonymity

will be maintained with adherence to professional standards of confidentiality and applicable laws. A file for each subject must be maintained that includes the signed ICF and all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents for the EDC.

Investigators are required to maintain all study documentation until notification by the Sponsor that any records may be discarded.

The Investigator is responsible for maintaining adequate case histories in each subject's source records.

13.3. SUBJECT CONFIDENTIALITY

All reports and subject samples will be identified only by the assigned subject number and initials, as applicable by local law, to maintain subject confidentiality. Additional subject confidentiality measures (as required by region) will be covered within the Clinical Trial Agreement for each site as applicable.

13.4. LIABILITY

In the event of a side effect or injury, appropriate medical care as determined by the Investigator, or his/her designated alternate will be provided.

If a bodily injury is sustained resulting directly from the Study Drug, the Sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury that is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and his/her staff. No other compensation of any type will be provided by the Sponsor. Compensation for lost wages, disability, or discomfort due to the study is not available.

13.5. ETHICAL AND LEGAL ISSUES

The Investigator and site personnel are responsible for conducting this study in accordance with the ICH, GCP, and all other applicable laws and regulations.

13.5.1. Institutional Review Board

The protocol, ICF, clinical sites and Investigators must be approved by an IRB before the study is initiated. The IRB must comply with U.S. CFR 21 Part 56 and local laws.

Documentation of approval by the designated central IRB will be provided to the Investigators. The Sponsor will:

- Obtain IRB approval of the protocol, ICF, advertisements to recruit subjects and IRB approval of any protocol amendments and ICF revisions before implementing the changes.
- Provide the IRB with any required information before or during the study.
- Submit progress reports to the IRB, as required, requesting additional review and approval, as needed; and provide copies of all relevant IRB communications to the Investigator.

The Investigator is responsible for:

- Notifying the IRB within 15 calendar days of all SAEs and unexpected AEs related to study medications.
- Obtaining approval by their institution's own IRB if the Investigator's institution has its own IRB.

13.6. INFORMED CONSENT FORM

The Sponsor will submit the ICF to the central IRB for approval. An IRB-approved copy of the ICF will be forwarded to the Investigator or site staff.

The ICF documents study-specific information the Investigator provides to the subject and the subject's agreement to participate. The Investigator explains in plain terms the nature of the study along with the aims, methods, anticipated benefits, potential risks, and any discomfort that participation may entail. The ICF must be signed and dated before the subject enters the study. The original ICF and any amended ICF, signed and dated, must be retained in the subject's file at the study site and a copy must be given to the subject.

14. INVESTIGATOR RESPONSIBILITIES

The Investigator agrees to:

- Conduct the study in accordance with the protocol, except to protect the safety, rights, or welfare of subjects.
- Personally conduct or supervise the study.
- Ensure that requirements for obtaining informed consent and IRB review and approval comply with ICH, CFR 21 Parts 50 and 56 and local laws.
- Report to the Sponsor any AEs that occur during the study in accordance with ICH, CFR 21 Part 312.64 and local laws.

- Read and understand the Investigator's Brochure including potential risks and side effects of the drug.
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate records in accordance with ICH, 21 CFR Part 312.62, and local laws and have records available for inspection by the Sponsor, FDA, or other authorized agency.
- Promptly report to the IRB and the Sponsor all changes in research activity and unanticipated problems involving risks to subjects or others (including amendments and expedited safety reports).
- Comply with all other requirements regarding obligations of Clinical Investigators and all other pertinent requirements listed in ICH, 21 CFR Part 312 and local laws.

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16. APPENDIX A – SCHEDULE OF ACTIVITIES

Procedures	Screening Period -60 Days to 0	Baseline Visit (Study Day 1)	Week 4	Week 16	Week 28	Week 40	Week 52	Week 64	Week 76 ET/ED[7]	Safety Follow-up[13]
Informed Consent	X									
I/E Criteria	X	X								
Medical & Surgical History	X									
Adverse Events	X	X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	
Physical Examination	X[1]	X	X	X	X	X	X	X	X	
Neurologic Examination	X[1]	X	X	X	X	X	X	X	X	
Height	X									
Weight	X	X	X	X	X	X	X	X	X	
Resting ECG	X	X[14]	X			X			X	
Biochemistry, Hematology, Urinalysis	X	X	X	X	X	X	X	X	X	
Urine Drug Screen	X									
TSH, free T4, B12, HBsAg, HCV-Ab	X									
HbA1C (diabetic subjects only)	X									
Plasma P-tau181 or P-tau217	X[12]									
Genotyping sample		X								
MRI	X					X[2]			X[2]	
Plasma Biomarkers	X[3]				X[3]		X[3]		X[3]	
Plasma PK					X[11]				X[11]	
CSF Biomarkers	X[4]								X[4]	
Amyloid PET	X[5]								X[5]	
Tau PET	X[6]								X[6]	
MMSE	X				X		X		X	
CDR	X								X	

Procedures	Screening Period -60 Days to 0	Baseline Visit (Study Day 1)	Week 4	Week 16	Week 28	Week 40	Week 52	Week 64	Week 76 ET/ED[7]	Safety Follow-up[13]
Geriatric Depression Scale	X									
ADAS-Cog12		X	X	X	X	X	X	X	X	
ADCS-ADL		X	X	X	X	X	X	X	X	
NPI		X			X		X		X	
ZBI		X	X	X	X	X	X	X	X	
C-SSRS	X[8]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	
Drug Dispensation		X[10]	X	X	X[10]	X	X	X		
Drug Accountability			X	X	X	X	X	X	X	
End of Study Follow-up Phone Call										X

1. Complete Physical and Neurologic Examinations during the Screening Period only, brief examinations thereafter
2. MRI sub-study subjects only (150 subjects total; 50 subjects/group)
3. Plasma biomarker sub-study subjects only; these are the same subjects in both PET sub-studies (270 subjects total; 90 subjects/group). Collection of blood samples can be taken on Day 1 prior to administration of first Study Drug dose.
4. CSF biomarker sub-study subjects only (90 subjects total; 30 subjects/group)
5. Amyloid PET sub-study subjects only (120 subjects total; 40 subjects/group)
6. Tau PET sub-study subjects only (150 subjects total; 50 subjects/group)
7. Early Termination / Early Discontinuation subjects do not need to complete the electronic clinical outcome assessments if performed within 30 days of the ET/ED Visit
8. During the Screening Period, the C-SSRS Baseline/Screening version will be administered
9. At Study Day 1, as well as all remaining visits, the C-SSRS Since Last Visit version will be administered
10. The first dose of Study Drug is administered at the clinic to all subjects on Study Day 1; for tau PET sub-study participants only at the Week 28 visit, administer Study Drug after plasma PK sample is collected
11. Plasma PK sample from tau PET sub-study participants only
12. Plasma P-tau181 or plasma P-tau217 not required if the subject has evidence for AD pathophysiology prior to Screening visit
13. This phone call will thus occur Week 77 to 78 for those subjects who complete all study visits, or 1 to 2 weeks after Early Termination. If the subject reports an adverse event, the subject should be followed and treated by the Investigator until the AE has resolved or stabilized.
14. ECG on Study Day 1 collected in triplicate

CLINICAL RESEARCH PROTOCOL

PROTOCOL PTl-125-06

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 76-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF TWO DOSES OF SIMUFILAM IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE

SPONSOR:

CASSAVA SCIENCES, INC.
7801 N. Capital of Texas Highway, Suite 260
Austin, TX 78731
Phone: 512-501-2444

This clinical study is supported by NIH grant AG073350.

Confidentiality

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 76-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF TWO DOSES OF SIMUFILAM IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE

Approvals:

[redacted]

20 July 2021
Date

SVP, Neuroscience
Cassava Sciences, Inc.

[redacted]

20 July 2021
Date

Chief Clinical Development Officer
Cassava Sciences, Inc.

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 76-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF TWO DOSES OF SIMUFILAM IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE

Signature of Agreement for Protocol PTI-125-06

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practice (GCP) and complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR Part 312.

[redacted] 20/JUL/2021

Coordinating Principal Investigator Signature Date

[redacted]

Print Coordinating Principal Investigator Name

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1. LIST OF ABBREVIATIONS

3xTg	triple transgenic
α7nAChR	α7 nicotinic acetylcholine receptor
$A\beta_{42}$	amyloid $beta_{1-42}$
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADME	absorption, distribution, metabolism, excretion
AE	Adverse Event
ALT	alanine transaminase
ALP	alkaline phosphatase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
BMI	Body Mass Index
BUN	blood urea nitrogen
CDR-GS	Clinical Dementia Rating – Global Score
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
CSF	cerebrospinal fluid
CSI	Cassava Sciences, Inc.
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computerized tomography
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FLNA	filamin A
GCP	good clinical practice
GDS	Geriatric Depression Scale
GGT	gamma glutamyl transpeptidase
GLP	good laboratory practice

hERG	human ether-a-go-go-related gene
iADRS	Integrated Alzheimer's Disease Rating Scale
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	insulin receptor
IRB	independent review board
ISLT	International Shopping List Test
LDH	lactose dehydrogenase
LOQ	limit of quantitation
MCI	mild cognitive impairment
MEMS	Medication Event Monitoring System
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NIA - AA	National Institute on Aging - Alzheimer's Association
NMDAR	N-methyl D-aspartate receptor
NOAEL	no observable adverse effect level
NOEL	no observable effect level
NPI	Neuropsychiatric Inventory
PAL	Paired Associate Learning
PET	positron emission tomography
PK	pharmacokinetics
PTI-125	former name of simufilam
SavaDx	blood-based diagnostic/biomarker candidate
RBC	red blood cell
SAE	serious adverse event
SOP	standard operating procedure
Tmax	time to Cmax
ULN	upper limit of normal
WBC	white blood cell
YKL40	chitinase-like protein 1, a secreted glycoprotein associated with inflammation and tissue remodeling
ZBI	Zarit Burden Interview

2. INTRODUCTION

2.1. MECHANISM OF ACTION

Cassava Sciences, Inc. is developing simufilam, a novel drug candidate designed to treat and slow the progression of Alzheimer's disease (AD). Simufilam binds with femtomolar affinity to an altered conformation of filamin A (FLNA) that is induced by beta amyloid$_{1-42}$ (Aβ_{42}), present in AD brain and critical to the toxicity of Aβ_{42}.[1-3] Simufilam binding reverses the altered FLNA conformation and restores FLNA's native shape, preventing two toxic signaling cascades of Aβ_{42}. Aβ_{42}, in monomer or small oligomer form, hijacks the α7-nicotinic acetylcholine receptor (α7nAChR) and signals via this receptor to hyperphosphorylate tau. This signaling requires the recruitment of altered FLNA to this receptor. In addition, altered FLNA also links to toll-like receptor 4 (TLR4) to allow Aβ_{42} to persistently activate this receptor, leading to inflammatory cytokine release and neuroinflammation. Normal FLNA does not associate with either α7nAChR or TLR4. In addition to disrupting the normal functions of α7nAChR and tau protein, Aβ_{42}'s toxic signaling to hyperphosphorylate tau leads to the signature tangles in AD brain. In two AD mouse models and in postmortem human AD brain tissue, simufilam restored function of three receptors that are impaired in AD: the α7nAChR, the N-methyl-D-aspartate receptor (NMDAR), and the insulin receptor (IR).[2,3] Simufilam also improved synaptic plasticity and reduced tau hyperphosphorylation, amyloid deposits, neurofibrillary tangles and inflammatory cytokine release.[2,3] We therefore expect simufilam both to improve cognition and to slow AD progression. Both mouse models used a dose of 20 mg/kg/day (equivalent to 60 mg/m^2/day).

2.2. SAFETY PHARMACOLOGY AND TOXICOLOGY

A robust nonclinical ADME, safety pharmacology, and general and genetic toxicology program has been conducted with simufilam. *In vitro* metabolic profiling showed minimal metabolism across several species including humans. Simufilam was rapidly absorbed and eliminated in *in vivo* studies in rat and dog with nearly 100% oral bioavailability, a 2.67-h half-life in dog, dose-proportional PK and no accumulation. Simufilam does not inhibit or induce major CYP450 enzymes, nor is a substrate or inhibitor of major human drug transporters at clinically relevant concentrations. Safety pharmacology studies showed no adverse effects on gross behavioral and physiological parameters in the Irwin test of CNS toxicity in rats, no adverse effects on respiratory rate, tidal volume or minute volume in the rat respiratory test, and no adverse effects on arterial blood pressure, heart rate and ECG parameters in the dog cardiovascular study. The *in vitro* hERG test for cardiotoxicity also indicated no adverse effect. A full battery of genotoxicity studies was conducted (*in vitro* bacterial Ames, *in vitro* chromosomal aberration, and *in vivo* rat micronucleus test) and all

were negative. An *in vitro* specificity screen showed no significant activation or inhibition of a panel of 68 receptors, channels and transporters.

Simufilam was tested in single dose and repeat dose oral toxicity studies of up to 6 months in rats and 9 months in dogs. A 6-month repeat dose oral toxicity study in rats (PTI-125-NC-049) used the same doses as a 28-day study (50, 500 and 1000 mg/kg/day), which found 500 mg/kg/day to be the no-adverse-effect-level (NOAEL). In the 6-month study, the toxicological response was characterized by decreased body weights and adverse structural and functional alterations in the liver of 500 and 1000 mg/kg/day animals, including increased hepatic weight, hepatocellular hypertrophy and vacuolation, single/multiple basophilic/ eosinophilic/clear cell focus, hepatocellular degeneration, pigmentation, and oval cell hyperplasia. The presence of bile pigment was consistent with cholestasis. These findings correlated with changes to the clinical chemistry profile, including increased ALP and total/direct bilirubin. Over the 1-month recovery period, there was complete recovery of the hepatocellular degeneration and partial recovery of hepatocellular hypertrophy; other microscopic findings in the liver remained. The NOAEL in this 6-month study was 50 mg/kg/day (equivalent to 300 mg/m^2), corresponding to a safety margin of 6- and 1.6-fold based on C_{max} and AUC over the 100 mg b.i.d. dose in human subjects. A second 6-month repeat dose oral toxicity study in rats determined the 6-month NOAEL in the rat to be < 125 mg/kg/day, based on hepatocellular vacuolation in both sexes and hepatocellular hypertrophy in females at 125 and 250 mg/kg. We are evaluating whether these liver effects are rat specific.

In a 9-month toxicity study in dogs (PTI-125-NC-050), the no-effect-level (NOEL) of simufilam was 25 mg/kg. The high dose of 200 mg/kg/day was decreased to 150 mg/kg/day after 1 month due to bodyweight loss considered unsustainable for 9 months. Clinical signs were slight hypoactivity and incidences of slight muscle fasciculations early in the study, and salivation. There were no pathology findings, but the high dose was considered adverse due to two unexplained deaths. The 75 mg/kg/day NOAEL (equivalent to 1500 mg/m^2) provides 38- and 19-fold safety margins based on C_{max} and AUC over the 100 mg b.i.d. dose in subjects.

Simufilam showed no mutagenic or clastogenic responses in a standard battery of genotoxicity assays.

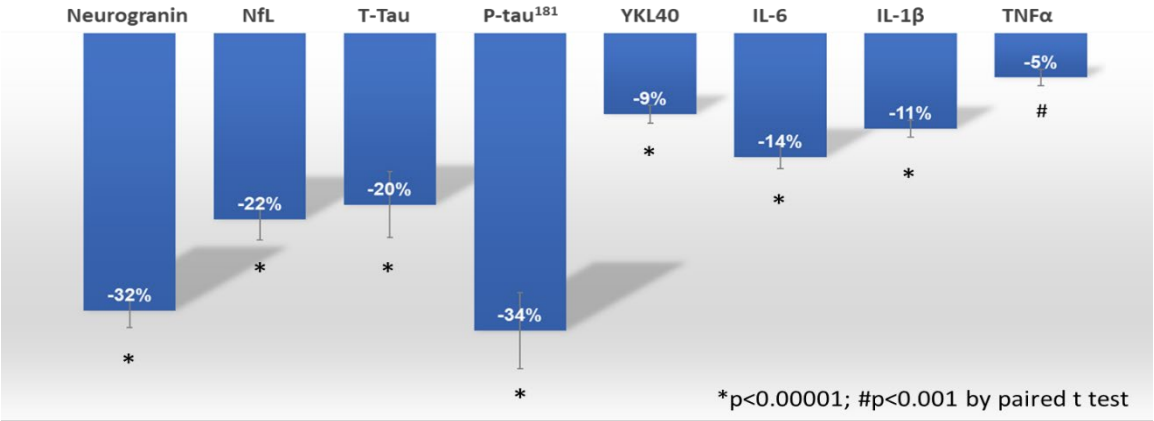
2.3. CLINICAL STUDIES

A first-in-human, double-blind, single ascending dose clinical study (PTI-125-01) was conducted in healthy normal volunteers, age 18-45 with oral dosing solution. Doses were placebo, 50, 100 and 200 mg (equivalent to 31, 62, and 123 mg/m^2, respectively) administered to three different groups of volunteers. The study showed dose proportional

PK, a half-life ranging from 4.5 to 6 h, and there were no drug-related adverse events (AEs).

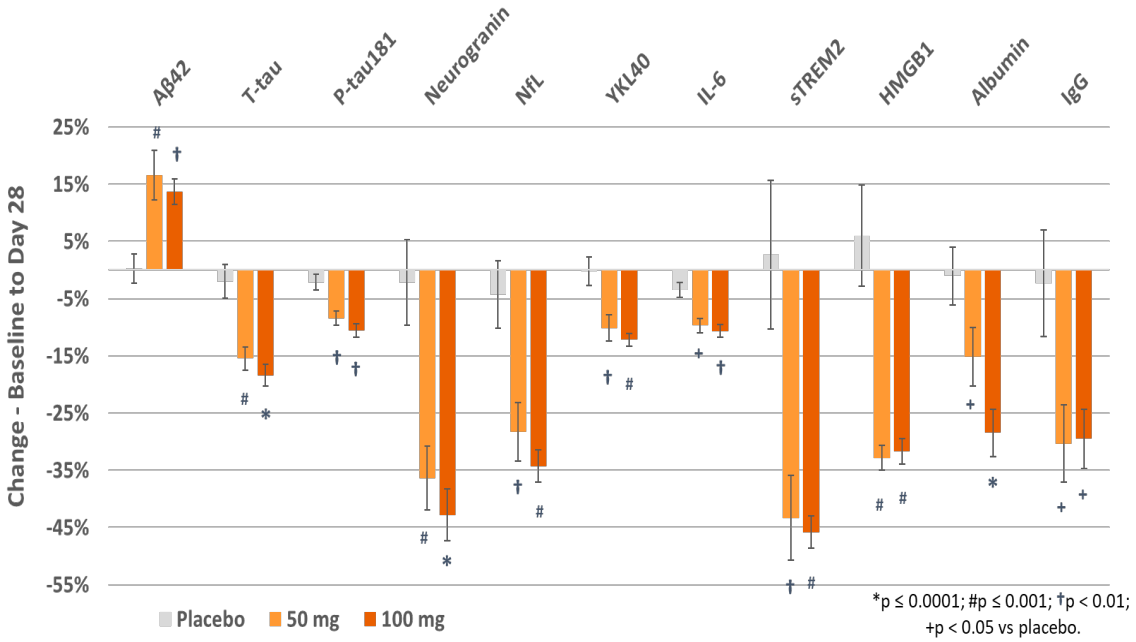
In a 28-day phase 2a study (PTI-125-03), 13 subjects with mild-to-moderate AD received simufilam 100 mg b.i.d. as oral tablets. Subjects had Mini-Mental State Exam (MMSE) scores ≥ 16 and ≤ 24, and were age 50-85 with a CSF total tau/$A\beta_{42}$ ratio ≥ 0.30. A second CSF sample was collected on Day 28, allowing assessment of change from baseline in biomarkers using commercial ELISA kits. All 8 biomarkers that are elevated in AD were significantly reduced from baseline (**Fig. 1**).[4] $A\beta_{42}$, which is low in AD, was increased slightly but non-significantly. Reduced inflammatory cytokines and YKL-40 indicated reduced neuroinflammation. A reduced neurodegenerative drive was suggested by reductions in neurogranin, neurofilament light chain, and total tau. The robust reduction in phospho-tau (P-tau181) confirms the mechanism of action of simufilam. Simufilam was safe and well tolerated in all subjects.

Figure 1. Phase 2a Mean Change from Baseline to Day 28 in CSF biomarkers (±SEM)



A phase 2b randomized, placebo-controlled clinical study (PTI-125-02) of simufilam 50 or 100 mg tablets or placebo (1:1:1) enrolled 64 mild-to-moderate AD subjects with MMSE 16-26. Both 50 and 100 mg doses significantly improved eleven CSF biomarkers of AD pathology, neurodegeneration, neuroinflammation and blood-brain barrier integrity (**Fig. 2**). CSF biomarker analyses were conducted blind to treatment and timepoint by an outside lab, and screening and Day 28 samples for each subject were measured in triplicate in the same ELISA plates. Albumin and immunoglobulin G (IgG) were measured by immunoblotting and quantified by densitometric quantitation. These data suggest disease modification and replicate Phase 2a results in a well-controlled study.

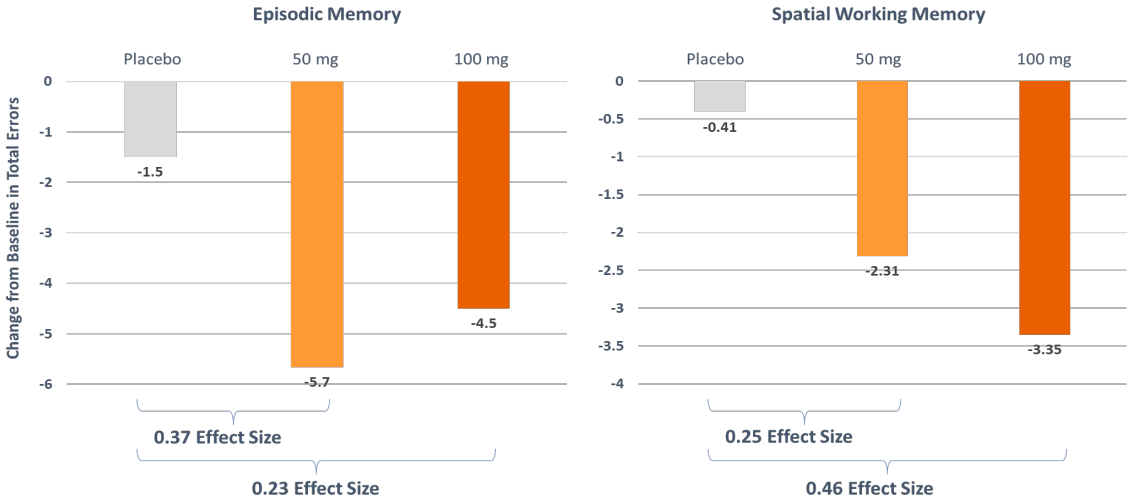
Figure 2. Phase 2b Mean Change from Baseline to Day 28 in CSF biomarkers (±SEM)



The secondary endpoints in the Phase 2b study were two cognitive measures using the Cambridge Neuropsychological Test Automated Battery. Subjects were assessed on the Paired Associate Learning (PAL) test, measuring episodic memory, and a test of spatial working memory. The primary outcome measure for each was total errors, with errors imputed for more difficult levels not reached in the PAL test. Simufilam produced encouraging effect sizes (calculated by Hedge's g for group sizes of 20), suggesting cognitive enhancement (**Fig. 3**). Effect sizes versus placebo for the test of episodic memory were 0.37 and 0.23 for the 50 and 100 mg groups, respectively, after removing the most and least impaired subjects by baseline score. For spatial working memory, effect sizes were 0.25 and 0.46 for these respective dose groups. Cognitive enhancement by simufilam is supported by preclinical data showing improved function of α7nAChR, NMDAR and insulin receptors and improved synaptic plasticity in 3xTg AD mice and in postmortem human AD brain tissue.

In both Phase 2 clinical studies, simufilam was well tolerated and no subjects discontinued due to AEs.

Figure 3. Phase 2b Mean Change from Baseline to Day 28 in Total Errors in Memory Test



3. STUDY OBJECTIVES

The primary objective of this study is to investigate the safety and efficacy of simufilam in slowing cognitive and functional decline following 76-week, repeat-dose oral administration in mild-to-moderate AD subjects, 50-87 years of age. Secondary objectives are to assess neuropsychiatric symptoms and to replicate the CSF biomarker effects observed in the two Phase 2 studies (PTI-125-03 and PTI-125-02) after 76 weeks of simufilam treatment. A third objective is to investigate the effect of simufilam treatment on plasma biomarkers as well as anatomical correlates of disease progression (brain volume [hippocampus, ventricles and whole brain]; amyloid and tau deposition in the brain).

4. SUMMARY OF STUDY DESIGN

In this Phase 3 clinical study, approximately 1,083 subjects with mild-to-moderate AD (361 per arm) will receive placebo or 50 mg tablets of simufilam or 100 mg tablets of simufilam, twice daily, for 76 weeks. Randomization (1:1:1) will be stratified by low or high MMSE (16-20 and 21-27).

Subjects, 50-87 years of age, will be selected for screening based on a diagnosis of AD consistent with Stages 4 or 5 on the Alzheimer's continuum (National Institute on Aging – Alzheimer's Association 2018[5]). Subjects must have MMSE $\geq$ 16 and $\leq$ 27, and a Clinical Dementia Rating Global Score (CDR-GS) of 0.5, 1 or 2. Finally, subjects must have

confirmed PET or fluid biomarker evidence of AD pathophysiology prior to randomization (see Section 5.2 – Inclusion Criteria for details).

Once subjects have been satisfactorily screened for study participation, visits to the research clinic will occur on Study Day 1 and at Weeks 4, 16, 28, 40, 52, 64 and 76.

The co-primary endpoints include the 12-item Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog12) and the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), both assessed as the change from baseline to the end of the double-blind treatment period (Week 76).

Secondary endpoints include the integrated Alzheimer's Disease Rating Scale (iADRS), Neuropsychiatric Inventory (NPI), MMSE, and Clinical Dementia Rating Sum of Boxes (CDR-SB). A brief questionnaire assessing caregiver burden, the Zarit Burden Interview (ZBI), will be collected as an additional secondary endpoint.

Safety will be evaluated by adverse event monitoring, vital signs, clinical labs, and the Columbia Suicide Severity Rating Scale (C-SSRS) at every visit. All subjects will undergo MRI during screening to ensure entry criteria are met, however, 150 subjects (50 subjects per treatment group) will also undergo repeat MRI assessments at Weeks 40 and 76 to assess both long-term safety and drug impact on brain volume as noted above. ECGs will be conducted Day 1 and Weeks 4, 40 and 76. A complete physical and neurological examination will be performed at screening, and brief examinations will be performed at all other visits. Weight will be measured during the Screening Period, on Study Day 1 and at all other visits.

A limited number of research sites will be invited to participate in one or more sub-studies to assess the impact of simufilam on anatomical and biomarker endpoints, including: change from baseline in CSF biomarkers (30 subjects/group), brain volume via MRI (50 subjects/group), and amyloid and tau PET (40 and 50 subjects/group, respectively). Participants in both PET sub-studies will provide plasma for a biomarker sub-study, and those in the tau PET sub-study will also provide additional plasma for a PK exposure-response analysis. Changes from baseline for these imaging and fluid biomarkers represent additional secondary endpoints.

The ninety subjects (30 per group) in the CSF sub-study will undergo lumbar puncture during the Screening Period and again at the Week 76 End-of-Treatment Visit to collect CSF biomarkers.

An independent Data Safety Monitoring Board (DSMB) will meet periodically to review subject safety assessments and determine if dosing may continue. A charter will be developed with specific guidance for the DSMB.

5. SUBJECT SELECTION

5.1. STUDY POPULATION

Approximately 1,083 subjects will be enrolled in the study.

5.2. INCLUSION CRITERIA

Each subject must meet the following Inclusion Criteria:

1. Capable of providing either written informed consent or, if incapable of written consent, permission to participate can be obtained from a legally authorized representative. Verbal assent to the study procedures and schedule is required of all participants. Genotyping for apolipoprotein E (ApoE) will be included in the informed consent, and participants must consent to this to be included in the study. If, in the Investigator's judgment, a subject loses capacity to consent during the duration of the study, a legally authorized representative must consent on behalf of the subject. All consent processes must be undertaken prior to any study procedures.

2. Age ≥ 50 and ≤ 87 years at the time of the informed consent, male or female.

3. Meets National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework criteria (2018) for individuals in clinical Stage 4 or Stage 5 of the Alzheimer's continuum.[5]

4. The subject and/or study partner report a gradual and progressive change in memory for ≥ 6 months.

5. Evidence for AD pathophysiology, confirmed either prior to or during the screening period prior to randomization, as follows:

    a. Prior to screening, confirmed with appropriate documentation by either: 1) CSF total tau/$A\beta_{42}$ ratio (must be ≥ 0.28), or 2) an abnormal amyloid or tau positron emission tomography (PET) scan consistent with AD; or

    b. During screening, subjects must demonstrate an elevated plasma P-tau181 level (a research biomarker that identifies AD pathophysiology with high accuracy; see lab manual for details).

6. MMSE score ≥ 16 and ≤ 27 at screening.

7. CDR-GS must be 0.5, 1 or 2.

8. If female, either surgically sterile or postmenopausal for at least 1 year.

9. Male subjects must be willing to use contraception during the study. With female partners of childbearing potential, male subjects, regardless of their fertility status, must agree to either remain abstinent or use condoms in combination with one additional highly effective method of contraception (e.g., oral or implanted contraceptives, or intrauterine devices) or an effective method of contraception (e.g., diaphragms with spermicide or cervical sponges) during the study and for 14 days after study drug dosing has been completed.

10. Fluency in a language of the research site and the utilized assessment materials.

11. Has adequate visual and auditory acuity (in the Investigator's judgment) that is sufficient to complete all scheduled assessments (eyeglasses and hearing aids are permitted).

12. If receiving background AD medications, including cholinesterase inhibitors, memantine, neuroleptics, antidepressants, anxiolytics, or sleep medications, the dosing regimen must be stable for at least 12 weeks prior to Study Day 1 (randomization) and should be expected to remain stable during the study (Note – barbiturates, meprobamate, and high dose benzodiazepines are not allowed, while low dose benzodiazepines, zolpidem, zaleplon and suvorexant are permitted).

13. The subject has not been a smoker or chewed tobacco for at least 3 years.

14. Availability of a person (a study partner) who, in the Investigator's opinion, has frequent and sufficient contact with the study subject (defined as ≥10 hours per week), and can:

    a. provide accurate information regarding the study subject's cognitive and functional abilities,

    b. agree to comply with and participate at all scheduled visits and study procedures,

    c. sign the necessary consent form,

    d. maintain the same level of interaction with the study subject throughout the study duration.

15. Individuals who have participated in a clinical study with an investigational drug targeting the underlying AD process are permitted to participate in this study on a case-by-case basis after consultation between the Principal Investigator and the Sponsor (subjects known to have been randomized to placebo do not require such consultation

and are permitted to participate).

5.3. EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

1. Residence in a skilled nursing facility requiring 24-hour care (Note – subjects may reside in an assisted living facility if they do not need 24-hour care).

2. Any contraindications to study procedures (e.g., potential subjects with a pacemaker must be excluded due to the required MRI during screening).

3. A medical condition or treatment with an anticoagulant that would interfere with a lumbar puncture for those subjects being considered for participation in the CSF biomarker assessment.

4. BMI < 18.5 or > 35.0

5. Evidence of a neurologic condition other than AD that, in the judgment of the Investigator, significantly contributes to the subject's dementia, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, Huntington's disease, or normal pressure hydrocephalus.

6. Subjects with any current primary psychiatric diagnosis other than AD if, in the judgment of the Investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the subject's ability either to comply with study procedures or to complete the study. Patients with a history of schizophrenia or chronic psychosis are excluded.

7. Geriatric Depression Scale (15-item) score > 8.

8. Affirms suicidal ideation in response to questions number 4 or 5 in the C-SSRS during the past 3 months (i.e., "active suicidal ideation with some intent to act, without specific plan," or "active suicidal ideation with specific plan and intent") or affirms any of the questions contained in the Suicidal Behavior section of the C-SSRS as applicable during the past 12 months.

9. Meets DSM-V criteria for alcohol or substance use disorder within 2 years before the Screening Period.

10. MRI presence of cerebral vascular pathology (including, but not limited to, hemorrhage, infarct > 1 cm^3, or > 3 lacunar infarcts), cerebral contusion, symptomatic

subdural hematoma, aneurysm, or space-occupying lesion deemed clinically significant in the opinion of the Investigator.

11. History of transient ischemic attack (TIA) or stroke within 12 months of screening, or history of a stroke concurrent with the onset of dementia.

12. History of seizure within 12 months of screening.

13. History of severe head trauma; history of head trauma with loss of consciousness > 10 min within 12 months of screening; history of head trauma concurrent with the onset of dementia; history of head trauma likely to be contributing to the subject's cognitive impairment in the Investigator's judgment.

14. Onset of dementia secondary to cardiac arrest, surgery with general anesthesia, or resuscitation.

15. Clinically significant, untreated or inadequately treated sleep apnea that is likely to be contributing to the subject's cognitive impairment in the Investigator's judgment.

16. Insufficiently controlled diabetes mellitus, defined as:

    a. requiring insulin treatment (unless subject has been stable for at least 4 weeks prior to screening on a once-daily dose of long-acting insulin), or

    b. HbA1C > 8.0% during the Screening Period.

17. Malignant tumor within 3 years before screening (except definitively treated squamous or basal cell carcinoma, cervical carcinoma in situ, localized non-progressive prostate cancer, localized stage 1 bladder cancer or colon polyp resolved by excision, per judgment of the Investigator).

18. Known positive HIV status.

19. Positive HBsAg or HCV-Ab during screen.

20. Positive urine drug screen for substances of abuse.

21. Vitamin B12 level lower than the normal limit at the time of screening (and that remains below on repeat testing). Subjects may be enrolled following initiation of B12 therapy for at least 4 weeks prior to randomization with confirmation of a normal level upon repeat testing.

22. Thyroid-stimulating hormone (TSH) levels greater than the upper limit of normal and a free thyroxine (free T4) lower than the lower limit of normal; subjects on thyroid

supplementation for hypothyroidism must be on a stable dose for ≥ 3 months before screening.

23. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – subjects with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN).

24. History or diagnosis of clinically significant ischemic heart disease (e.g., myocardial infarction or unstable angina within 1 year of screening), moderate to severe congestive heart failure, cardiomyopathy, myocarditis or valvular heart disease of clinical significance in the Investigator's judgment.

25. History of or current clinically significant cardiac arrhythmia or heart block as evidenced by ECG in the judgment of the Investigator.

26. Clinically significant abnormality on screening electrocardiogram (ECG), including, but not necessarily limited to, a confirmed QT interval by the Fridericia correction formula (QTcF) > 470 msec (females) or > 450 msec (males) based on WHO 2016 guidelines.

27. Insufficiently controlled hypertension (defined, at rest, as systolic BP > 160 mmHg or diastolic BP > 100 mmHg; if an initial BP reading is elevated, an additional measurement during the Screening Period could be used before excluding a potential subject for insufficiently controlled hypertension).

28. Hypotension (systolic BP < 90 mmHg) or bradycardia with a heart rate less than 50 beats per minute during screening (out of range values may be repeated once for confirmation).

29. Use of medications that in the Investigator's opinion will contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or other study procedures.

30. Donepezil > 10 mg/day, currently or within 12 weeks of Study Day 1 (randomization).

31. Discontinued AChEI < 12 weeks prior to randomization.

32. Administration of aducanumab, either currently or previously prescribed (Note – administration of aducanumab at any point during this clinical study is prohibited).

33. Antipsychotics (Note – low doses are allowed only if given for sleep disturbances,

agitation, aggression or dementia-related psychosis, and only if the dose has been stable for at least 4 weeks prior to screening).

34. Tricyclic antidepressants and monoamine oxidase inhibitors if prescribed within 4 weeks prior to screening; all other antidepressants are allowed only if the dose has been stable for at least 4 weeks prior to screening.

35. Immunosuppressants, including systemic corticosteroids, if taken in clinically immunosuppressive doses (steroid use for allergy or inflammation is permitted).

36. Use of antiepileptic medications if taken for control of seizures (Note – use of antiepileptic medications are allowed if used for mood stabilization).

37. Chronic intake of opioid-containing analgesics.

38. Use of prescribed sedating H1 antihistamines.

39. Use of nicotine therapy (all dosage forms including a patch), varenicline (Chantix), or similar therapeutic agent within 4 weeks prior to screening.

40. Loss of a significant volume of blood (> 450 mL) within 4 weeks of randomization.

41. COVID-19 infection within 3 months of screening (Note – the subject must be fully vaccinated for COVID-19 at least two weeks prior to Study Day 1 [randomization] if there is no history of a prior COVID-19 infection).

42. Clinically significant abnormalities on screening laboratory tests in the judgment of the Investigator.

43. Unstable medical condition that is clinically significant in the judgment of the Investigator, including significant neurologic, hepatic, renal, endocrinologic, cardiovascular, gastrointestinal, pulmonary, hematologic, immunologic or metabolic disease.

44. Any other medical or neurological condition (other than Alzheimer's disease), that, in the opinion of the Investigator, might represent a contributing cause to the subject's cognitive impairment, or affect cognitive assessment, subject safety, ability to comply with study assessments, drug compliance and completion of the study.

6. STUDY DRUG

6.1. SIMUFILAM PHYSICAL DESCRIPTION AND PREPARATION

Investigational simufilam and matching placebo will be supplied by Cassava as coated tablets including 50 and 100 milligram active strengths.

All remaining unused simufilam study drug will be returned to the Sponsor or designee.

6.1.1 Packaging and Labeling

Simufilam or placebo tablets in plastic bottles will be supplied in 70-count bottles for a 4-week supply or 188-count bottles for a 12-week supply. Bottles include a desiccant canister and are closed with a foil seal and child-resistant (CR) cap. Each bottle contains 7 or 10 days of extra medication to accommodate scheduling flexibility with clinic visits.

A Medication Event Monitoring System (MEMS®) that is 21 CFR Part 11 compliant will be used to track adherence to the b.i.d. dosing schedule. MEMS® caps will be supplied to replace the conventional CR cap on each bottle. One (1) MEMS cap will be assigned to each subject for use throughout the study. Each MEMS cap has an LCD display that provides immediate visual indication of the number of doses taken that day and the number of hours since the prior dose that day, resetting to zero each night. Instructions on management and use of MEMS caps will be provided in the Pharmacy manual and during site training.

Each bottle is labeled with a unique double-blind ID number that is randomly assigned to a treatment. A computer-based clinical study management system will specify the bottle ID number to be dispensed according to the subject's treatment randomization.

6.1.2 Storage

The investigational drug supplies must be stored in a locked cabinet or room with limited access at controlled room temperature, 20-25º C (68-77º F) and protected from moisture.

6.1.3 Drug Accountability

The Investigator will be responsible for monitoring the receipt, storage, dispensing and accounting of all study medications according to site standard operating procedures (SOPs). All records documenting the chain of custody for the study medication must be retained in the site study file. Accurate, original site records must be maintained of drug inventory and dispensing. All records must be made available to the Sponsor (or designee) and appropriate regulatory agencies upon request.

6.2. ADMINISTRATION AND DOSING REGIMEN

Subjects will be randomized to receive placebo, or 50 mg or 100 mg simufilam b.i.d. (approximately 361 subjects per treatment group). Study drug can be taken with or without food.

6.3. CONCOMITANT MEDICATIONS

Use of prescription or non-prescription medications will be recorded during the study. Chronic medications must be stable for 4 weeks prior to screening [Note – see Inclusion Criterion #12 and Exclusion Criteria #30 and #31 for additional details regarding background medications frequently prescribed to patients with AD].

7. STUDY PROCEDURES

Appendix A presents the Schedule of Activities.

Prior to any study-related activities, the Informed Consent Form (ICF) must be signed and dated by the subject (or a legally authorized representative) and the study partner. The format and content of the ICF must be agreed upon by the Principal Investigator(s), the appropriate IRB and the Sponsor. The signed and dated ICF must be retained by the Investigator in the subject's file.

7.1. EVALUATIONS BY VISIT

Follow-up visits can be scheduled ± five (5) days from the targeted Study Visit date.

7.1.1. Screening Period (No greater than a 60-day duration prior to Study Day 1)

The Sponsor recognizes the Screening Period assessments and procedures may not necessarily be completed in a single visit. A subject is permitted to be screened over more than one calendar day if, in the Investigator's judgment, such scheduling will optimize the accuracy of Screening Period assessments and procedures. The following will be completed during the Screening Period:

- Informed Consent.
- Review of Inclusion and Exclusion Criteria
- Collect demographic information (e.g., sex, date of birth, race/ethnicity, years of education)
- Medical and surgical history

- Review concomitant medications, and any discontinued medications, in the 4 weeks prior to screening
- To the extent such information is available, review and record any investigational drugs administered during past clinical study participation regardless of the date of such participation
- History of drug, alcohol and tobacco use
- eCOA order of administration at screening:
  - MMSE
  - CDR
  - Geriatric Depression Scale
  - C-SSRS – Baseline/screening version
- Complete physical and neurologic examination; including measurement of key vital signs (blood pressure [supine], temperature, pulse rate), height and weight (to calculate BMI)
- A 12-lead ECG (5-min supine)
- Laboratory assessments, including: routine serum chemistry, TSH, free T4, Vitamin B12 levels, HBsAg, HCV-Ab, hematology, urinalysis and urine screen for drugs of abuse. Plasma for P-tau181 assessment will also be collected unless there is documented evidence of AD pathophysiology prior to screening. For subjects with diabetes, collect a blood sample for HbA1C.
- Once the clinical and laboratory assessments above have been completed and verified to be consistent with study participation, schedule brain MRI to confirm subject meets MRI-specific entry criteria (Note –previous brain MRI results, with appropriate documentation, will be accepted for up to 6 months prior to the Study Day 1 Visit unless a recent clinical event warrants a repeat scan).
  - Subjects participating in the MRI sub-study assessment of brain volume (150 total; 50 subjects/group), including the hippocampus, ventricles and whole brain, will have, in addition to the MRI during the Screening Period, subsequent MRI scans at Weeks 40 and 76.

7.1.2. Sub-studies with PET and fluid biomarkers

Selected research sites will participate in additional sub-study assessments to determine the effect of simufilam on anatomical and biomarker secondary endpoints.

- Subjects participating in either amyloid or tau PET sub-studies (40 and 50 subjects/group, respectively) will be scheduled for their first PET scan prior to Study Day 1; they will undergo the procedure again at Week 76. Individual subjects can potentially participate in both PET imaging sub-studies, but consideration must be given to total radiation exposure based on the number of PET scans and dose each subject would receive per annum. Moreover, PET scans using different tracers must also be acquired at least 24 hours apart to ensure adequate wash-out of the previous tracer prior to new tracer administration.
- Subjects participating in the PET sub-studies will also have blood samples drawn for assessments of plasma-based biomarkers during the Screening Period and again at Weeks 28, 52 and 76 (270 total; 90 subjects/group). Subjects participating in the tau PET sub-study will also provide a plasma sample for PK at Weeks 28 and 76.
- Subjects participating in an assessment of CSF biomarkers (90 total; 30 subjects/group) will undergo lumbar puncture prior to Study Day 1 and again at Week 76.

7.1.3. Rescreening of a Subject

Individuals who have given informed consent and fail to meet the Inclusion and/or Exclusion criteria (screen failure) may not be rescreened if the screen failure is due to non-eligible MMSE (<16), MRI or P-tau181 results. If screen failure occurs for the following reasons, the subject is allowed one rescreen:

- Low vitamin B12 requiring supplemental therapy (can rescreen after 4 weeks)
- MMSE of 28 (can rescreen after 8 weeks)

Other reasons for screen failure will require Sponsor approval to rescreen.

7.1.4. Study Day 1 (Dosing Initiation)

Subjects will come to the clinic in the morning. Prior to dosing, the following assessments will be conducted:

- Confirmation of Inclusion/Exclusion criteria
- Confirm subject has been fully vaccinated for COVID-19 for at least two weeks if there is no history of a prior COVID-19 infection
- Review of concomitant medications
- Adverse Event Monitoring
- Vital signs (blood pressure [supine], temperature, pulse).
- Weight
- Brief physical and neurologic examination (Note: the brief physical and neurologic examination performed on Study Day 1 and at all subsequent visits will include an assessment of the following: general appearance; cardiovascular, pulmonary, and abdominal examination, as well as an examination of any other system in response to subject-reported symptoms; cranial nerves [II-XII], tone, power, deep tendon reflexes, coordination and gait)
- eCOA order of administration:
  - ADAS-Cog12
  - ADCS-ADL
  - NPI
  - ZBI
  - C-SSRS – Since Last Visit version
- ECG
- Clinical laboratory tests (blood and urine)
- Genotyping for ApoE

Once all Study Day 1 procedures and assessments have been completed, the subject is randomized to a treatment and the bottle of Study Drug to be dispensed is assigned by the computer-based study management system. A Medication Event Monitoring System (MEMS®) cap is drawn from stock for permanent assignment to the subject and initialized via the computer interface. Before removing Study Drug from the bottle, remove the original closure and apply the MEMS cap as a replacement. Just prior to administering the first dose of Study Drug, remove the MEMS cap and remove one (1) tablet.

Subjects will be administered Study Drug at least 1 hour before leaving the clinic. The subject will be discharged with their supply of Study Drug. The study partner will be trained on the features and proper use of the MEMS cap and instructed to administer Study Drug twice daily with or without food. The study partner should be advised that a dose can be up to 4 h late, but, if a dose is missed, the next dose should NOT be doubled.

Information and instruction for the computer-based study management system, and the MEMS cap will be covered during site training, and written reference information will be included in the pharmacy manual.

For all follow-up visits, subjects will be instructed to bring their Study Drug bottle to the clinic. At each visit, the MEMS cap will be read into the computer-based study management system to inform the site about the subject's Study Drug adherence. The MEMS cap will be removed from the returned bottle and applied to the newly dispensed bottle of Study Drug.

7.1.5. Weeks 4, 16, 40 and 64 Follow-up Visits

Subjects will return to clinic for these scheduled visits within a ± 5-day "window."

- Vital signs (blood pressure [supine], temperature and pulse)
- Weight
- Brief physical and neurologic examination
- Adverse event monitoring
- Use of concomitant medications
- eCOA order of administration:
  - ADAS-Cog12 (whenever possible, within 1 h of the time of day administered at the Study Day 1 Visit, and by the same rater)
  - ADCS-ADL
  - ZBI
  - C-SSRS – Since Last Visit version
- Clinical laboratory tests (blood and urine)
- Weeks 4 and 40 only: resting ECG

- Week 40 only: for those 150 subjects participating in the MRI sub-study to determine the effect of simufilam on brain volume, schedule their Week 40 scan.

7.1.6. Weeks 28 and 52 Follow-up Visit

Subjects will return to clinic for these scheduled visits within a ± 5-day "window." On the Week 28 Visit, subjects in the tau PET sub-study should come to the clinic before taking their a.m. dose and have their PK blood sample collected prior to their dose.

- Vital signs (blood pressure [supine], temperature and pulse)
- Weight
- Brief physical and neurologic examination
- Adverse event monitoring
- Use of concomitant medications
- eCOA order of administration:
  - ADAS-Cog12 (whenever possible, within 1 h of the time of day administered at the Study Day 1 Visit, and by the same rater)
  - ADCS-ADL
  - MMSE
  - NPI
  - ZBI
  - C-SSRS – Since Last Visit version
- Clinical laboratory tests (blood and urine)
- For those 270 subjects participating in the amyloid or tau PET and plasma biomarker sub-studies, collect their Week 28 and Week 52 blood samples (including PK at Week 28 for those in the tau PET sub-study)

7.1.7. Week 76 End-of-Treatment Visit / Early Termination (ET) Visit

Subjects will return to clinic for this scheduled visit within a ± 5-day "window." Subjects in the tau PET sub-study should **not** take an a.m. dose prior to their blood draw.

- Vital signs (blood pressure [supine], temperature and pulse)

- Weight
- Brief physical and neurologic examination
- Adverse Event monitoring
- Use of concomitant medications
- eCOA order of administration:
    - ADAS-Cog12 (whenever possible, within 1 h of the time of day administered at the Study Day 1 Visit, and by the same rater)
    - ADCS-ADL
    - MMSE
    - CDR
    - NPI
    - ZBI
    - C-SSRS – Since Last Visit version
- Resting ECG
- Clinical laboratory tests (blood and urine)
- For those 270 subjects participating in the amyloid or tau PET and plasma biomarker sub-studies, collect their Week 76 blood samples (including PK samples for those in the tau PET sub-study) and schedule their Week 76 scan.
- For those 150 subjects participating in the MRI sub-study to determine the effect of simufilam on brain volume, schedule their Week 76 scan.
- For those 90 subjects participating in the CSF biomarker sub-study, perform a lumbar puncture to collect CSF (5 mL) after all other testing has been completed.

Note: Early Termination subjects do not need to complete the electronic Clinical Outcome Assessments if performed within 30 days of the ET Visit (see Section 9 – Early Discontinuation)

7.1.8. Week 77-78 End-of-Study Follow-up

The subject and/or study partner will receive a follow-up phone call 7-14 days after the last dose for adverse event monitoring. If needed, a follow-up clinic visit will be scheduled.

7.1.9. Treatment after Study Completion

The Sponsor plans to initiate an open-label extension study for subjects who have completed participation in Study PTI-125-06. Should a subject elect to participate in the open-label extension study, the End-of-Study Follow-up (Section 7.1.8) will not be conducted.

7.1.10. Unscheduled Visits and Discontinuation due to AEs

For unscheduled visits due to AEs, any assessments conducted will be at the discretion of the Investigator and pertinent to the AE. If a decision is made to discontinue the subject from study drug, the Sponsor will be notified immediately. The subject should be followed and treated by the Investigator until the AE has resolved or stabilized (see Section 10.1 – Adverse Events). Restarting the subject on study drug will be a mutual decision by the Investigator and the Sponsor. See also Section 9.0 – Early Discontinuation.

7.1.11. Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to ensure subject safety and to evaluate liver event etiology during administration of study drug. Potential discontinuation of study drug for abnormal liver function tests should be considered by the Investigator in consultation with the designated medical monitor if the study subject meets one or more of the following criteria:

- ALT or AST ≥ 4x ULN;
- ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN;
- ALT or AST ≥ 3x ULN if associated with the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia; or
- ALP elevations, if deemed of liver origin and drug-related as follows:
    - ALP > 3x ULN;
    - ALP > 2.5x ULN and total bilirubin > 2x ULN; or
    - ALP > 2.5x ULN if associated with the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia.

In the event of discontinuation due to abnormal liver function tests, the subject will be

appropriately investigated to determine the potential cause and referred to a physician experienced in the treatment of hepatic disorders.

Study drug should be discontinued if a subject: (1) positively affirms suicidal ideation in response to questions number 4 or 5 in the Suicidal Ideation section of the C-SSRS, or (2) reports any suicidal behavior or non-suicidal self-injurious behavior since their last visit in response to the C-SSRS Suicidal Behavior questions. The subject should be referred to a psychiatrist or an appropriate health care professional for further evaluation and management.

Bodyweight loss of ≥ 2 kg resulting in a BMI < 18.5 is an additional stopping criterion.

7.2. LABORATORY ASSESSMENTS

7.2.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed during the Screening Period, Study Day 1 pre-dose, and at all follow-up visits:

- Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count.
- Serum Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphate, blood urea nitrogen (BUN), total bilirubin, creatinine, albumin, globulin, total protein, uric acid, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), lactose dehydrogenase (LDH).
- Urinalysis: color, specific gravity, pH, protein, glucose, ketones, occult blood, nitrites and leukocyte esterase. A "reflex" microscopic examination will be performed if protein, occult blood, nitrites or leukocyte esterase is present on the basic analysis.
- Screening Period: During the Screening Period only, bloods will be drawn for TSH, free T4, Vitamin B12, HepBsAg, HCV-Ab, HbA1C (diabetic subjects only) and plasma P-tau181 (Note – plasma collection for P-tau181 not required if subject has documented evidence of AD pathophysiology prior to screening). Urine to screen for drugs of abuse (amphetamines, cocaine, opiates and phencyclindine) will also be collected during the Screening Period.

7.2.2. Collection of Whole Blood Samples for ApoE Genotyping

Whole blood samples for genotyping ApoE will be collected on Study Day 1 (please review instructions as per lab manual).

7.2.3. Preparation of Plasma Biomarker and PK Samples from PET Sub-study Participants

At each blood collection for biomarkers and PK, blood samples will be drawn into two Vacutainer® tubes (10 mL per tube) containing K2EDTA. The tubes will be placed on ice. Within 30 min of collection, the blood will be centrifuged at approximately 1000 X G for 15 min, preferably at 4-5°C. Within 30 min of centrifuging, plasma will be transferred to polypropylene tubes and stored at -70°C until shipped to the central lab (complete instructions as per lab manual).

7.2.4. CSF assays

CSF samples should be split, with approximately 2.5 mL shipped to the central lab (as instructed per lab manual). The remaining CSF will be retained at the study site and frozen at -70°C or below until instructions are received from the Sponsor.

CSF samples will be collected during the Screening Period and again at Week 76 for those subjects participating in the CSF biomarker sub-study. The biomarkers to be assayed will include:

- Total Tau
- P-tau181
- Neurogranin
- sTREM2
- Amyloid-beta 42
- Neurofilament light chain

8. COGNITIVE AND FUNCTIONAL ASSESSMENTS

8.1. MINI-MENTAL STATE EXAM (MMSE)

The MMSE[6] is a set of standardized questions covering several target areas: orientation, registration, attention and calculation, short-term verbal recall, naming, repetition, 3-step command, reading, writing, and visuospatial cognitive assessment. Administration of the MMSE is estimated to take approximately 10 minutes.

8.2. CLINICAL DEMENTIA RATING (CDR)

Washington University's CDR[7] characterizes six domains of cognitive and functional performance applicable to AD and related dementias: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The study partner is interviewed first by a qualified rater who assesses all six domains. The subject is then interviewed in the absence of the caregiver. A CDR global score can be calculated by accessing Washington University's online algorithm (https://biostat.wustl.edu/~adrc/cdrpgm/index.html) where 0 = no dementia, and scores of 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively. The sum of boxes (i.e., CDR-SB)[8] can also be calculated by summing the six individual domain scores. This detailed quantitative general index may provide more information than the CDR-GS in patients with mild dementia.

8.3. ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE SUBSCALE 12 (ADAS-COG12)

The ADAS-Cog[9,10] is a psychometrician-administered battery comprised of several cognitive domains including memory, comprehension, praxis, orientation, and spontaneous speech. The ADAS-Cog12 (which includes Delayed Word Recall) will be administered to all subjects at various key visits throughout the study.

8.4. NEUROPSYCHIATRIC INVENTORY (NPI)

A study partner interview, the 12-item NPI[11] records frequency and severity of common neuropsychiatric symptoms in dementia (Hallucinations, Delusions, Agitation/aggression, Dysphoria/depression, Anxiety, Irritability, Disinhibition, Euphoria, Apathy, Aberrant motor behavior, Sleep and nighttime behavior change, Appetite and eating change). The study partner is then asked to rate their own distress for the subject's behavioral symptoms occurring in the past 4 weeks.

8.5. ALZHEIMER'S DISEASE COOPERATIVE STUDY – ACTIVITIES OF DAILY LIVING (ADCS-ADL-AD)

The ADCS-ADL[12] is a 23-item study partner questionnaire that covers both basic activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal).

8.6. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

The C-SSRS[13] is an assessment tool used to assess the lifetime suicidality of a subject (C-

SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit).

8.7. ZARIT BURDEN INTERVIEW (ZBI)

The ZBI[14,15] is a 22-item scale designed to assess the stress or burden experienced by caregivers of people with dementia. The ZBI will be administered as an interview with the caregiver. The scale consists of 22 statements reflecting how people can feel when taking care of another person. The statements are phrased as questions for the caregiver to indicate how often they feel the way described in the statement. The 5 possible responses for each item are Never, Rarely, Sometimes, Quite Frequently, and Nearly Always.

8.8. GERIATRIC DEPRESSION SCALE (GDS)

The GDS[16] is a 30-item yes/no question test designed to screen for depression in elderly persons. The GDS short form (15-items)[17] version utilized in this study will be clinician administered with caregiver input. Subjects will be evaluated for symptoms of depression during the Screening Period.

8.9. ELECTRONIC CAPTURE OF RATING SCALES

The assessments MMSE, CDR, ADAS-Cog12, GDS, NPI, ADCS-ADL, C-SSRS, and ZBI will be captured electronically by an eCOA platform that is 21 CFR Part 11 compliant. Data collected by eCOA will be transferred directly to the EDC vendor's database.

9. EARLY DISCONTINUATION

Subjects may choose to discontinue study drug or study participation at any time, for any reason, and without prejudice. Moreover, a subject may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral or administrative reasons. Discontinued subjects should be followed according to medical practice standards, and the outcome documented. Follow-up is required if the subject is discontinued due to an adverse event (AE). Any comments (spontaneous or elicited) or complaints made by the subject and the reason for termination and the date of stopping the drug must be recorded in the Case Report Form (CRF) and source documents.

The following must be completed and documented in the source documents and CRFs for all subjects who discontinue the study early:

- The reason for early study discontinuation. If the subject is withdrawn for more than one reason, each reason should be documented in the source documents and the most clinically relevant reason should be entered on the CRF.

- Vital signs (blood pressure, temperature and pulse), brief physical and neurologic examination, weight, clinical laboratory tests, ECG, use of concomitant medications and adverse events should be obtained at discharge prior to release.
- Blood draw for plasma biomarkers
- ADAS-Cog, MMSE, CDR, ADCS-ADL, NPI, ZBI and C-SSRS (as detailed in Section 7.1.7 – Early Termination Visit), if not performed within the last 30 days.

10. ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

10.1. ADVERSE EVENTS - DEFINITION

An Adverse Event (AE) is any undesirable event that occurs to a subject during a study, whether or not that event is considered study drug-related. Monitoring for AEs will start at dosing. Examples include:

- Any treatment-emergent signs and symptoms (events that are marked by a change from the subject's baseline/entry status [e.g., an increase in severity or frequency of pre-existing abnormality or disorder])
- All reactions from study drug, an overdose, abuse of drug, withdrawal phenomena, sensitivity or toxicity to study drug
- Apparently unrelated illnesses
- Injury or accidents (Note: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate medical events [e.g., for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately])
- Extensions or exacerbations of symptoms, subjective subject-reported events, new clinically significant abnormalities in clinical laboratory, physiological testing or physical examination

All AEs, whether or not related to the study drug, must be fully and completely documented on the AE page of the CRF and in the subject's clinical chart.

In the event that a subject is withdrawn from the study because of an AE, it must be recorded on the CRF as such. The subject should be followed and treated by the

Investigator until the abnormal parameter or symptom has resolved or stabilized.

The Investigator must report all directly observed AEs and all spontaneously reported AEs. The Investigator will ask the subject a non-specific question (e.g., "Have you noticed anything different since your dose of the study medication?") to assess whether any AEs have been experienced since the last assessment. AEs will be identified and documented in the Electronic Data Capture (EDC) system in appropriate medical terminology. The severity and the relationship to the study drug will be determined and reported in EDC (see below).

10.2. Adverse Events - Severity Rating

The severity of each AE should be characterized and then classified into one of three clearly defined categories as follows:

- Mild – the AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.
- Moderate – the AE produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment.
- Severe – the AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

These three categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's report and the physician's observations. The severity of the AE should be recorded in the appropriate section of the EDC.

10.3. Adverse Events – Relationship to Study Drug

The relationship of each AE to the study drug will be classified into one of three defined categories as follows:

- Unlikely – a causal relationship between the AE and the study drug is unlikely.
- Possible – a causal relationship between the AE and the study drug is possible.
- Probable – a causal relationship between the AE and the study drug is probable. For example, the AE is a common adverse event known to occur with the pharmacological class of the study drug; or the AE abated on study drug discontinuation and reappeared upon rechallenge with the study drug.

These three categories are based on the Investigator's clinical judgment, which in turn

depends on consideration of various factors such as the subject's report, the timing of the AE in relationship to study drug administration/discontinuation, the physician's observations and the physician's prior experience. The relationship of the AE to the study drug will be recorded in the appropriate section of the EDC.

10.4. SERIOUS ADVERSE EVENTS AND UNEXPECTED ADVERSE EVENTS - DEFINITIONS

A Serious Adverse Event (SAE) includes (but is not limited to) an experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (i.e., the subject is at immediate risk of death from the reaction as it occurs). "Life-threatening" does not include an event that, had it occurred in a more serious form, might have caused death. For example, drug- induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
- In-patient hospitalization (hospital admission, not an emergency room visit) or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity (i.e., a substantial disruption of the subject's ability to carry out normal life functions).
- A congenital anomaly/birth defect.

In addition, medical and scientific judgment should be exercised in deciding whether other situations should be considered an SAE (i.e., important medical events that may not be immediately life-threatening or result in death but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above). Examples of such medical events include (but are not limited to): allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

An **unexpected** AE is one for which the specificity or severity is not consistent with the current Investigator's Brochure. For example, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure listed only elevated hepatic enzymes or hepatitis.

Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by

virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

10.5. SERIOUS ADVERSE EVENTS REPORTING

The reporting of SAEs by the Sponsor to regulatory authorities (e.g., FDA) is a regulatory requirement. Each regulatory agency has established a timetable for reporting SAEs based upon established criteria. Likewise, it is the responsibility of the Principal Investigator to report SAEs to the IRB.

All SAEs must be reported immediately **(within 24 h of learning of the event)** by e-mail to:

Premier Research Global Pharmacovigilance
[redacted]

Do not delay reporting a suspected SAE to obtain additional information. Any additional information, if collected, can be reported to the Sponsor as a follow-up to the initial report.

SAEs must be immediately reported to the responsible IRB.

In the case of a death or other SAE that has occurred within 30 days after receiving study drug, the Principal Investigator must also report such an event within 24 hours of being notified. Your local IRB may also require these reports.

In the event of any SAE (other than death), the subject will be instructed to contact the study physician (Principal Investigator or designee) using the phone number provided in the Informed Consent Form. All subjects experiencing an SAE will be seen by a Principal Investigator or designee as soon as feasible following the report of an SAE.

11. STATISTICAL CONSIDERATIONS

11.1. RANDOMIZATION

Randomized treatments will be assigned by subject numbers in a randomly generated numeric sequence.

The randomization code will not be revealed to study subjects, Investigators, clinical staff, study monitors or the Sponsor until all subjects have completed therapy and the database has been finalized and locked.

Under normal circumstances, the blind should not be broken. The blind may be broken

only if specific emergency treatment is indicated. The date, time and reason for the unblinding must be documented in the CRFs, and the medical monitor must be informed as soon as possible.

11.2. ANALYSIS POPULATIONS

The Intent-To-Treat (ITT) analysis set includes all randomized subjects. All efficacy analyses will be conducted in this analysis set and subjects will be included in the group to which they were randomized.

The Safety analysis set includes all subjects who receive study treatment. All safety analyses will be completed in the Safety analysis set and subjects will be included in the group based on the treatment actually received.

11.3. STATISTICAL ANALYSIS

11.3.1. Primary Efficacy Analysis

Each of the two co-primary endpoints will be analyzed using a linear mixed model for repeated measurements. The dependent variable is the change from baseline and the model will include fixed effects for treatment group (three levels), week (7 levels, corresponding to Weeks 4, 16, 28, 40, 52, 64 and 76), the treatment group-by-week interaction, and the randomization stratification variable. The baseline value of the corresponding endpoint will be included as a covariate and the unstructured covariance model will be used. The Study Day 1 ADAS-Cog12 and ADCS-ADL assessments will represent the baseline value for these variables.

For each of the two co-primary endpoints, the primary analysis will compare the 100 mg group and the placebo group at Week 76 using a two-sided test at the alpha = 0.05 level of significance. Study success requires that both co-primary comparisons are statistically significant.

11.3.2 Key Secondary Analysis

If both primary comparisons are statistically significant, then the corresponding comparisons at Week 76 for the 50 mg group versus the placebo group will be tested at the alpha = 0.05 level of significance (two-sided).

11.3.3 Other Secondary Analyses

The iADRS[18,19] is a linear combination of scores from two well-established, widely accepted, therapeutically sensitive measures of AD: the ADAS-Cog and ADCS-iADL (the

instrumental component of the ADCS-ADL). The iADRS has been validated and statistical properties of the composite performance have been described[20]. All items of the ADAS-Cog12 and the ADCS-iADL will be included to generate this primary efficacy composite measurement without additional weighting.

Secondary clinical endpoint data (iADRS, NPI, MMSE and ZBI) measured repeatedly will be analyzed by linear mixed models for repeated measurements, as described above for the primary analysis.

Plasma assays may include P-tau181, SavaDx, neurofilament light chain and other biomarkers. All plasma biomarker data and MRI data measured repeatedly will be analyzed by linear mixed models for repeated measurements, as described above for the primary analysis.

CSF biomarker endpoints to be analyzed include: 1) neurogranin, 2) neurofilament light chain, 3) total tau, 4) P-tau181, 5) sTREM2, and 6) $A\beta_{42}$. Additional CSF biomarkers may be measured. All CSF biomarker data, PET imaging data and CDR-SB will be analyzed using ANCOVA models with treatment group as a factor and the baseline value of the corresponding endpoint as a covariate.

All secondary analyses will be conducted using two-sided tests at the alpha = 0.05 level of significance, with no adjustments for multiplicity.

11.4. SAFETY ANALYSIS

Adverse events reported on case report forms will be mapped to preferred terms and organ systems using the MedDRA mapping system. Vital signs and clinical laboratory results will be descriptively summarized in terms of change from screening values.

11.5. SAMPLE SIZE

Approximately 1,083 subjects will be enrolled in this study. The sample size was determined by a power analysis of ADAS-Cog in a similar population over 76 weeks. This analysis determined that the comparison between an active arm and placebo requires group sizes of 289 to provide 90% power to detect a 45% difference from placebo at 76 weeks, based on the use of a two-sided test at the alpha = 0.05 significance level. The power calculation assumes a true mean change from baseline for placebo of 6.0 points and a standard deviation of 10.0 points. Assuming a drop-out of 20%, each treatment group should enroll 361 subjects.

12. STUDY TERMINATION

The study will be terminated following completion of the study or at any time at the discretion of the Sponsor.

13. DATA COLLECTION, RETENTION AND MONITORING

13.1. CASE REPORT FORMS

The CRF will be provided as an Electronic Data Capture (EDC) system that will serve as the collection method for subject data. The subjects in the study will not be identified by name on any study documents to be collected by the Sponsor (or CRO designee) but will be identified by a unique subject number.

All clinical information requested in this protocol will be recorded in the EDC system. It is strongly recommended that data entry be completed within 48 h of a subject's visit. In case of error noted on paper source documents, the correction will be noted, initialed and dated.

EDC data must be reviewed and verified for accuracy and signed-off by the staff personnel before database lock. Paper source documents, if used, will remain at the Investigator's site at the completion of the study.

13.2. AVAILABILITY AND RETENTION OF INVESTIGATIONAL RECORDS

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee) and Regulatory Agency (e.g., FDA) inspectors upon request. To assure accuracy of data collected in the EDC, it is mandatory that Sponsor representatives have access to original source documents (e.g., subject records, subject charts, and laboratory reports). During review of these documents, the subject's anonymity will be maintained with adherence to professional standards of confidentiality and applicable laws. A file for each subject must be maintained that includes the signed ICF and all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents for the EDC.

Investigators are required to maintain all study documentation until notification by the Sponsor that any records may be discarded.

The Investigator is responsible for maintaining adequate case histories in each subject's source records.

13.3. SUBJECT CONFIDENTIALITY

All reports and subject samples will be identified only by the assigned subject number and initials, as applicable by local law, to maintain subject confidentiality. Additional subject confidentiality measures (as required by region) will be covered within the Clinical Trial Agreement for each site as applicable.

13.4. LIABILITY

In the event of a side effect or injury, appropriate medical care as determined by the Investigator or his/her designated alternate will be provided.

If a bodily injury is sustained resulting directly from the Study Drug, the Sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury that is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and his/her staff. No other compensation of any type will be provided by the Sponsor. Compensation for lost wages, disability or discomfort due to the study is not available.

13.5. ETHICAL AND LEGAL ISSUES

The Investigator and site personnel are responsible for conducting this study in accordance with the ICH, GCP, and all other applicable laws and regulations.

13.5.1. Institutional Review Board

The protocol, ICF, clinical sites and Investigators must be approved by an IRB before the study is initiated. The IRB must comply with U.S. CFR 21 Part 56 and local laws.

Documentation of approval by the designated central IRB will be provided to the Investigators. The Sponsor will:

- Obtain IRB approval of the protocol, ICF, advertisements to recruit subjects and IRB approval of any protocol amendments and ICF revisions before implementing the changes.
- Provide the IRB with any required information before or during the study.
- Submit progress reports to the IRB, as required, requesting additional review and approval, as needed; and provide copies of all relevant IRB communications to the Investigator.

The Investigator is responsible for:

- Notifying the IRB within 15 calendar days of all SAEs and unexpected AEs related to study medications.
- Obtaining approval by their institution's own IRB, if the Investigator's institution has its own IRB.

13.6. INFORMED CONSENT FORM

The Sponsor will submit the ICF to the central IRB for approval. An IRB-approved copy of the ICF will be forwarded to the Investigator or site staff.

The ICF documents study-specific information the Investigator provides to the subject and the subject's agreement to participate. The Investigator explains in plain terms the nature of the study along with the aims, methods, anticipated benefits, potential risks, and any discomfort that participation may entail. The ICF must be signed and dated before the subject enters the study. The original ICF and any amended ICF, signed and dated, must be retained in the subject's file at the study site and a copy must be given to the subject.

14. INVESTIGATOR RESPONSIBILITIES

The Investigator agrees to:

- Conduct the study in accordance with the protocol, except to protect the safety, rights, or welfare of subjects.
- Personally conduct or supervise the study.
- Ensure that requirements for obtaining informed consent and IRB review and approval comply with ICH, CFR 21 Parts 50 and 56 and local laws.
- Report to the Sponsor any AEs that occur during the study in accordance with ICH, CFR 21 Part 312.64 and local laws.
- Read and understand the Investigator's Brochure including potential risks and side effects of the drug.
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate records in accordance with ICH, 21 CFR Part 312.62, and local laws and have records available for inspection by the Sponsor, FDA, or other authorized agency.

- Promptly report to the IRB and the Sponsor all changes in research activity and unanticipated problems involving risks to subjects or others (including amendments and expedited safety reports).
- Comply with all other requirements regarding obligations of Clinical Investigators and all other pertinent requirements listed in ICH, 21 CFR Part 312 and local laws.

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16. APPENDIX A – SCHEDULE OF ACTIVITIES

Procedures	Screening Period -60 Days to 0	Baseline Day 1	Week 4	Week 16	Week 28	Week 40	Week 52	Week 64	Week 76 ET/ED[7]	Week 77 to 78
Informed Consent	X									
I/E Criteria	X	X								
Medical & Med History	X									
Adverse Events		X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	
Physical Examination	X[1]	X	X	X	X	X	X	X	X	
Neurologic Examination	X[1]	X	X	X	X	X	X	X	X	
Height	X									
Weight	X	X	X	X	X	X	X	X	X	
Geriatric Depression Scale	X									
Resting ECG	X	X	X			X			X	
Biochemistry, Hematology, Urinalysis	X	X	X	X	X	X	X	X	X	
Urine Drug Screen	X									
TSH, free T4, B12, HBsAg, HCV-Ab	X									
HbA1C (diabetic subjects only)	X									
Plasma P-tau181	X[12]									
Genotyping sample		X								
MRI	X					X[2]			X[2]	
Plasma Biomarkers	X[3]				X[3]		X[3]		X[3]	
Plasma PK					X[11]				X[11]	
CSF Biomarkers	X[4]								X[4]	
Amyloid PET	X[5]								X[5]	
Tau PET	X[6]								X[6]	
MMSE	X				X		X		X	

Procedures	Screening Period -60 Days to 0	Baseline Day 1	Week 4	Week 16	Week 28	Week 40	Week 52	Week 64	Week 76 ET/ED[7]	Week 77 to 78
ADAS-Cog12		X	X	X	X	X	X	X	X	
ADCS-ADL		X	X	X	X	X	X	X	X	
CDR	X								X	
NPI		X			X		X		X	
ZBI		X	X	X	X	X	X	X	X	
C-SSRS	X[8]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	
Drug Dispensation		X[10]	X	X	X[10]	X	X	X		
Drug Accountability			X	X	X	X	X	X	X	
End of Study Follow-up Phone Call										X

1. Complete Physical and Neurologic Examinations during the Screening Period only, brief examinations thereafter
2. MRI sub-study subjects only (150 subjects total; 50 subjects/group)
3. Plasma biomarker sub-study subjects only; these are the same subjects in both PET sub-studies (270 subjects total; 90 subjects/group)
4. CSF biomarker sub-study subjects only (90 subjects total; 30 subjects/group)
5. Amyloid PET sub-study subjects only (120 subjects total; 40 subjects/group)
6. Tau PET sub-study subjects only (150 subjects total; 50 subjects/group)
7. Early Termination / Early Discontinuation subjects do not need to complete the electronic clinical outcome assessments if performed within 30 days of the ET/ED Visit
8. During the Screening Period, the C-SSRS Baseline/Screening version will be administered
9. At Study Day 1, as well as all remaining visits, the C-SSRS Since Last Visit version will be administered
10. The first dose of Study Drug is administered at the clinic to all subjects on Study Day 1; for tau PET sub-study participants only at the Week 28 visit, administer Study Drug after plasma PK sample is collected
11. Plasma PK sample from tau PET sub-study participants only
12. Plasma P-tau181 not required if the subject has evidence for AD pathophysiology prior to screening

CLINICAL RESEARCH PROTOCOL

PROTOCOL PTl-125-06

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 76-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF TWO DOSES OF SIMUFILAM IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE

SPONSOR:

CASSAVA SCIENCES, INC.
7801 N. Capital of Texas Highway, Suite 260
Austin, TX 78731
Phone: 512-501-2444

This clinical study is supported by NIH grant AG073350.

Confidentiality

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 76-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF TWO DOSES OF SIMUFILAM IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE

Approvals:

[redacted]

30 June 2021

Date

SVP, Neuroscience
Cassava Sciences, Inc.

[redacted]

June 30 2021

Date

Chief Clinical Development Officer
Cassava Sciences, Inc.

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 76-WEEK STUDY EVALUATING THE SAFETY AND EFFICACY OF TWO DOSES OF SIMUFILAM IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE

Signature of Agreement for Protocol PTI-125-06

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practice (GCP) and complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR Part 312.

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Coordinating Principal Investigator Signature Date

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Print Coordinating Principal Investigator Name

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1. LIST OF ABBREVIATIONS

3xTg	triple transgenic
α7nAChR	α7 nicotinic acetylcholine receptor
$A\beta_{42}$	amyloid $beta_{1-42}$
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADME	absorption, distribution, metabolism, excretion
AE	Adverse Event
ALT	alanine transaminase
ALP	alkaline phosphatase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
BMI	Body Mass Index
BUN	blood urea nitrogen
CDR-GS	Clinical Dementia Rating – Global Score
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
CR-MEMS	Child-Resistant Medication Event Monitoring System
CSF	cerebrospinal fluid
CSI	Cassava Sciences, Inc.
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computerized tomography
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FLNA	filamin A
GCP	good clinical practice
GDS	Geriatric Depression Scale
GGT	gamma glutamyl transpeptidase

GLP	good laboratory practice
hERG	human ether-a-go-go-related gene
iADRS	Integrated Alzheimer's Disease Rating Scale
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	insulin receptor
IRB	independent review board
ISLT	International Shopping List Test
LDH	lactose dehydrogenase
LOQ	limit of quantitation
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NIA - AA	National Institute on Aging - Alzheimer's Association
NMDAR	N-methyl D-aspartate receptor
NOAEL	no observable adverse effect level
NOEL	no observable effect level
NPI	Neuropsychiatric Inventory
PAL	Paired Associate Learning
PET	positron emission tomography
PK	pharmacokinetics
PTI-125	former name of simufilam
SavaDx	blood-based diagnostic/biomarker candidate
RBC	red blood cell
SAE	serious adverse event
SOP	standard operating procedure
Tmax	time to Cmax
ULN	upper limit of normal
WBC	white blood cell
YKL40	chitinase-like protein 1, a secreted glycoprotein associated with inflammation and tissue remodeling
ZBI	Zarit Burden Interview

2. INTRODUCTION

2.1. MECHANISM OF ACTION

Cassava Sciences, Inc. is developing simufilam, a novel drug candidate designed to treat and slow the progression of Alzheimer's disease (AD). Simufilam binds with femtomolar affinity to an altered conformation of filamin A (FLNA) that is induced by beta amyloid$_{1-42}$ (Aβ_{42}), present in AD brain and critical to the toxicity of Aβ_{42}.[1-3] Simufilam binding reverses the altered FLNA conformation and restores FLNA's native shape, preventing two toxic signaling cascades of Aβ_{42}. Aβ_{42}, in monomer or small oligomer form, hijacks the α7-nicotinic acetylcholine receptor (α7nAChR) and signals via this receptor to hyperphosphorylate tau. This signaling requires the recruitment of altered FLNA to this receptor. In addition, altered FLNA also links to toll-like receptor 4 (TLR4) to allow Aβ_{42} to persistently activate this receptor, leading to inflammatory cytokine release and neuroinflammation. Normal FLNA does not associate with either α7nAChR or TLR4. In addition to disrupting the normal functions of α7nAChR and tau protein, Aβ_{42}'s toxic signaling to hyperphosphorylate tau leads to the signature tangles in AD brain. In two AD mouse models and in postmortem human AD brain tissue, simufilam restored function of three receptors that are impaired in AD: the α7nAChR, the N-methyl-D-aspartate receptor (NMDAR), and the insulin receptor (IR).[2,3] Simufilam also improved synaptic plasticity and reduced tau hyperphosphorylation, amyloid deposits, neurofibrillary tangles and inflammatory cytokine release.[2,3] We therefore expect simufilam both to improve cognition and to slow AD progression. Both mouse models used a dose of 20 mg/kg/day (equivalent to 60 mg/m^2/day).

2.2. SAFETY PHARMACOLOGY AND TOXICOLOGY

A robust nonclinical ADME, safety pharmacology, and general and genetic toxicology program has been conducted with simufilam. *In vitro* metabolic profiling showed minimal metabolism across several species including humans. Simufilam was rapidly absorbed and eliminated in *in vivo* studies in rat and dog with nearly 100% oral bioavailability, a 2.67-h half-life in dog, dose-proportional PK and no accumulation. Simufilam does not inhibit or induce major CYP450 enzymes, nor is a substrate or inhibitor of major human drug transporters at clinically relevant concentrations. Safety pharmacology studies showed no adverse effects on gross behavioral and physiological parameters in the Irwin test of CNS toxicity in rats, no adverse effects on respiratory rate, tidal volume or minute volume in the rat respiratory test, and no adverse effects on arterial blood pressure, heart rate and ECG parameters in the dog cardiovascular study. The *in vitro* hERG test for cardiotoxicity also indicated no adverse effect. A full battery of genotoxicity studies was conducted (*in vitro* bacterial Ames, *in vitro* chromosomal aberration, and *in vivo* rat micronucleus test) and all

were negative. An *in vitro* specificity screen showed no significant activation or inhibition of a panel of 68 receptors, channels and transporters.

Simufilam was tested in single dose and repeat dose oral toxicity studies of up to 6 months in rats and 9 months in dogs. A 6-month repeat dose oral toxicity study in rats (PTI-125-NC-049) used the same doses as a 28-day study (50, 500 and 1000 mg/kg/day), which found 500 mg/kg/day to be the no-adverse-effect-level (NOAEL). In the 6-month study, the toxicological response was characterized by decreased body weights and adverse structural and functional alterations in the liver of 500 and 1000 mg/kg/day animals, including increased hepatic weight, hepatocellular hypertrophy and vacuolation, single/multiple basophilic/ eosinophilic/clear cell focus, hepatocellular degeneration, pigmentation, and oval cell hyperplasia. The presence of bile pigment was consistent with cholestasis. These findings correlated with changes to the clinical chemistry profile, including increased ALP and total/direct bilirubin. Over the 1-month recovery period, there was complete recovery of the hepatocellular degeneration and partial recovery of hepatocellular hypertrophy; other microscopic findings in the liver remained. The NOAEL in this 6-month study was 50 mg/kg/day (equivalent to 300 mg/m^2), corresponding to a safety margin of 6- and 1.6-fold based on C_{max} and AUC over the 100 mg b.i.d. dose in human subjects. A second 6-month repeat dose oral toxicity study in rats determined the 6-month NOAEL in the rat to be < 125 mg/kg/day, based on hepatocellular vacuolation in both sexes and hepatocellular hypertrophy in females at 125 and 250 mg/kg. Additional work is planned to evaluate whether these liver effects are rat specific.

In a 9-month toxicity study in dogs (PTI-125-NC-050), the no-effect-level (NOEL) of simufilam was 25 mg/kg. The high dose of 200 mg/kg/day was decreased to 150 mg/kg/day after 1 month due to bodyweight loss considered unsustainable for 9 months. Clinical signs were slight hypoactivity and incidences of slight muscle fasciculations early in the study, and salivation. There were no pathology findings, but the high dose was considered adverse due to two unexplained deaths. The 75 mg/kg/day NOAEL (equivalent to 1500 mg/m^2) provides 38- and 19-fold safety margins based on C_{max} and AUC over the 100 mg b.i.d. dose in subjects.

Simufilam showed no mutagenic or clastogenic responses in a standard battery of genotoxicity assays.

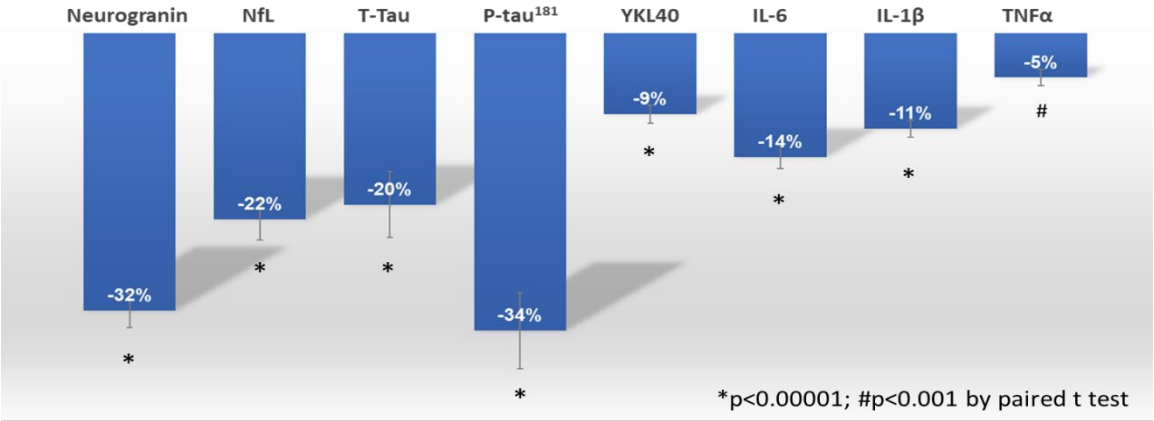
2.3. CLINICAL STUDIES

A first-in-human, double-blind, single ascending dose clinical study (PTI-125-01) was conducted in healthy normal volunteers, age 18-45 with oral dosing solution. Doses were placebo, 50, 100 and 200 mg (equivalent to 31, 62, and 123 mg/m^2, respectively) administered to three different groups of volunteers. The study showed dose proportional

PK, a half-life ranging from 4.5 to 6 h, and there were no drug-related adverse events (AEs).

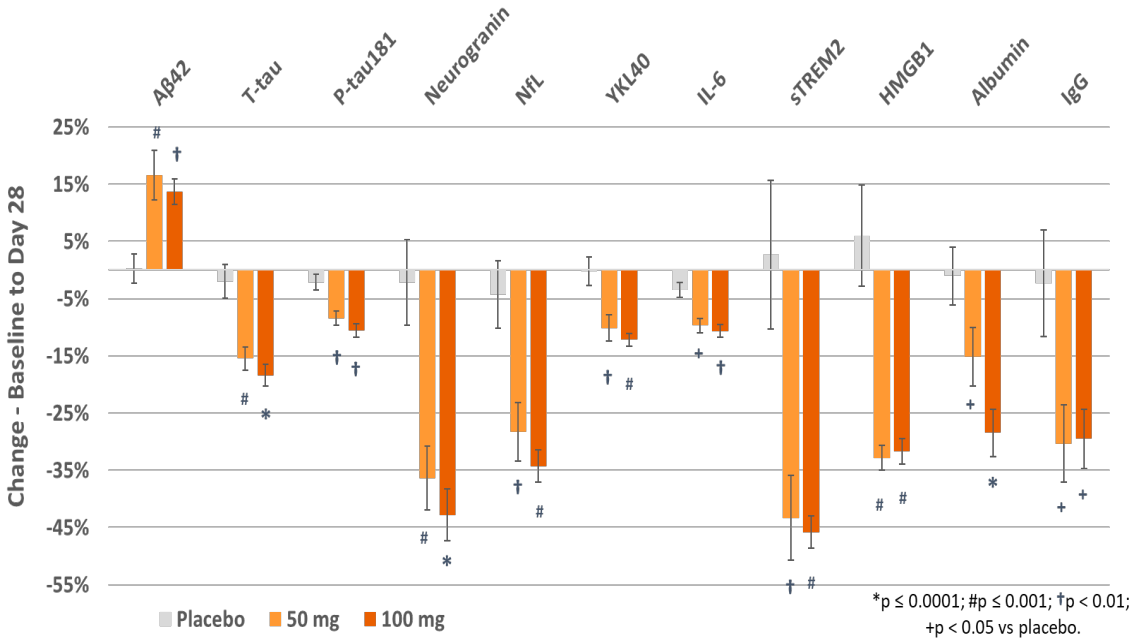
In a 28-day phase 2a study (PTI-125-03), 13 subjects with mild-to-moderate AD received simufilam 100 mg b.i.d. as oral tablets. Subjects had Mini-Mental State Exam (MMSE) scores ≥ 16 and ≤ 24, and were age 50-85 with a CSF total tau/Aβ42 ratio ≥ 0.30. A second CSF sample was collected on Day 28, allowing assessment of change from baseline in biomarkers using commercial ELISA kits. All 8 biomarkers that are elevated in AD were significantly reduced from baseline (**Fig. 1**).[4] Aβ42, which is low in AD, was increased slightly but non-significantly. Reduced inflammatory cytokines and YKL-40 indicated reduced neuroinflammation. A reduced neurodegenerative drive was suggested by reductions in neurogranin, neurofilament light chain, and total tau. The robust reduction in phospho-tau (P-tau181) confirms the mechanism of action of simufilam. Simufilam was safe and well tolerated in all subjects.

Figure 1. Phase 2a Mean Change from Baseline to Day 28 in CSF biomarkers (±SEM)



A phase 2b randomized, placebo-controlled clinical study (PTI-125-02) of simufilam 50 or 100 mg tablets or placebo (1:1:1) enrolled 64 mild-to-moderate AD subjects with MMSE 16-26. Both 50 and 100 mg doses significantly improved eleven CSF biomarkers of AD pathology, neurodegeneration, neuroinflammation and blood-brain barrier integrity (**Fig. 2**). CSF biomarker analyses were conducted blind to treatment and timepoint by an outside lab, and screening and Day 28 samples for each subject were measured in triplicate in the same ELISA plates. Albumin and immunoglobulin G (IgG) were measured by immunoblotting and quantified by densitometric quantitation. These data suggest disease modification and replicate Phase 2a results in a well-controlled study.

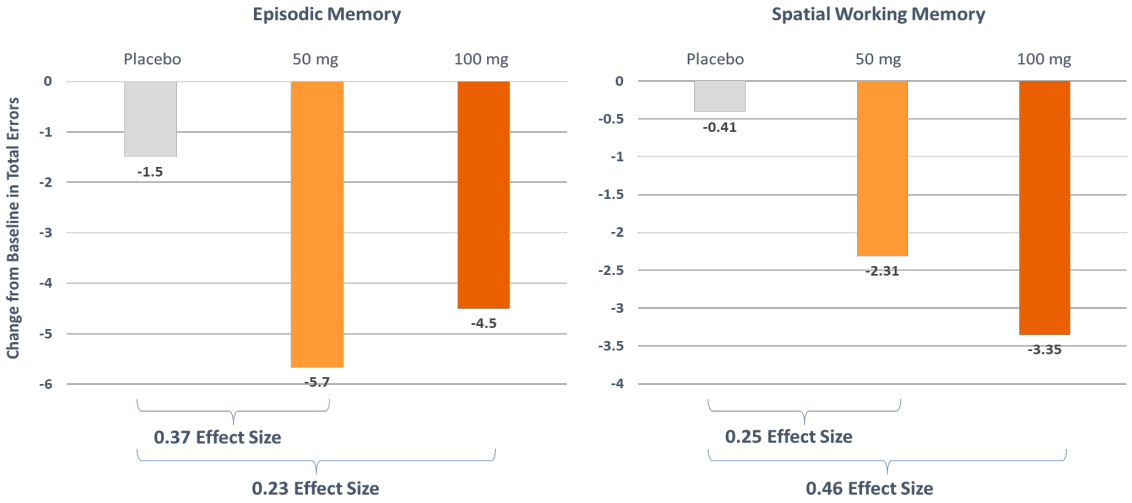
Figure 2. Phase 2b Mean Change from Baseline to Day 28 in CSF biomarkers (±SEM)



The secondary endpoints in the Phase 2b study were two cognitive measures using the Cambridge Neuropsychological Test Automated Battery. Subjects were assessed on the Paired Associate Learning (PAL) test, measuring episodic memory, and a test of spatial working memory. The primary outcome measure for each was total errors, with errors imputed for more difficult levels not reached in the PAL test. Simufilam produced encouraging effect sizes (calculated by Hedge's g for group sizes of 20), suggesting cognitive enhancement (**Fig. 3**). Effect sizes versus placebo for the test of episodic memory were 0.37 and 0.23 for the 50 and 100 mg groups, respectively, after removing the most and least impaired subjects by baseline score. For spatial working memory, effect sizes were 0.25 and 0.46 for these respective dose groups. Cognitive enhancement by simufilam is supported by preclinical data showing improved function of α7nAChR, NMDAR and insulin receptors and improved synaptic plasticity in 3xTg AD mice and in postmortem human AD brain tissue.

In both Phase 2 clinical studies, simufilam was well tolerated and no subjects discontinued due to AEs.

Figure 3. Phase 2b Mean Change from Baseline to Day 28 in Total Errors in Memory Test



3. STUDY OBJECTIVES

The primary objective of this study is to investigate the safety and efficacy of simufilam in slowing cognitive and functional decline following 76-week, repeat-dose oral administration in mild-to-moderate AD subjects, 50-87 years of age. Secondary objectives are to assess neuropsychiatric symptoms and to replicate the CSF biomarker effects observed in the two Phase 2 studies (PTI-125-03 and PTI-125-02) after 76 weeks of simufilam treatment. A third objective is to investigate the effect of simufilam treatment on plasma biomarkers as well as anatomical correlates of disease progression (brain volume [hippocampus, ventricles and whole brain]; amyloid and tau deposition in the brain).

4. SUMMARY OF STUDY DESIGN

In this Phase 3 clinical study, approximately 1,083 subjects with mild-to-moderate AD (361 per arm) will receive placebo or 50 mg tablets of simufilam or 100 mg tablets of simufilam, twice daily, for 76 weeks. Randomization (1:1:1) will be stratified by low or high MMSE (16-20 and 21-27).

Subjects, 50-87 years of age, will be selected for screening based on a diagnosis of AD consistent with Stages 4 or 5 on the Alzheimer's continuum (National Institute on Aging – Alzheimer's Association 2018[5]). Subjects must have MMSE $\geq$ 16 and $\leq$ 27, and a Clinical Dementia Rating Global Score (CDR-GS) of 0.5, 1 or 2. Finally, subjects must have

confirmed PET or fluid biomarker evidence of AD pathophysiology prior to randomization (see Section 5.2 – Inclusion Criteria for details).

Once subjects have been satisfactorily screened for study participation, visits to the research clinic will occur on Study Day 1 and at Weeks 4, 16, 28, 40, 52, 64 and 76.

The co-primary endpoints include the 12-item Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog12) and the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), both assessed as the change from baseline to the end of the double-blind treatment period (Week 76).

Secondary endpoints include the integrated Alzheimer's Disease Rating Scale (iADRS), Neuropsychiatric Inventory (NPI), MMSE, and Clinical Dementia Rating Sum of Boxes (CDR-SB). A brief questionnaire assessing caregiver burden, the Zarit Burden Interview (ZBI), will be collected as an additional secondary endpoint.

Safety will be evaluated by adverse event monitoring, vital signs, clinical labs, and the Columbia Suicide Severity Rating Scale (C-SSRS) at every visit. All subjects will undergo MRI during screening to ensure entry criteria are met, however, 150 subjects (50 subjects per treatment group) will also undergo repeat MRI assessments at Weeks 40 and 76 to assess both long-term safety and drug impact on brain volume as noted above. ECGs will be conducted Day 1 and Weeks 4, 40 and 76. A complete physical and neurological examination will be performed at screening, and brief examinations will be performed at all other visits. Weight will be measured during the Screening Period, on Study Day 1 and at all other visits.

A limited number of research sites will be invited to participate in one or more sub-studies to assess the impact of simufilam on anatomical and biomarker endpoints, including: change from baseline in CSF biomarkers (30 subjects/group), brain volume via MRI (50 subjects/group), and amyloid and tau PET (40 and 50 subjects/group, respectively). Participants in both PET sub-studies will provide plasma for a biomarker sub-study, and those in the tau PET sub-study will also provide additional plasma for a PK exposure-response analysis. Changes from baseline for these imaging and fluid biomarkers represent additional secondary endpoints.

The ninety subjects (30 per group) in the CSF sub-study will undergo lumbar puncture during the Screening Period and again at the Week 76 End-of-Treatment Visit to collect CSF biomarkers.

An independent Data Safety Monitoring Board (DSMB) will meet periodically to review subject safety assessments and determine if dosing may continue. A charter will be developed with specific guidance for the DSMB.

5. SUBJECT SELECTION

5.1. STUDY POPULATION

Approximately 1,083 subjects will be enrolled in the study.

5.2. INCLUSION CRITERIA

Each subject must meet the following Inclusion Criteria:

1. Capable of providing either written informed consent or, if incapable of written consent, permission to participate can be obtained from a legally authorized representative. Verbal assent to the study procedures and schedule is required of all participants. Genotyping for apolipoprotein E (ApoE) will be included in the informed consent, and participants must consent to this to be included in the study. If, in the Investigator's judgment, a subject loses capacity to consent during the duration of the study, a legally authorized representative must consent on behalf of the subject. All consent processes must be undertaken prior to any study procedures.

2. Age ≥ 50 and ≤ 87 years at the time of the informed consent, male or female.

3. Meets National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework criteria (2018) for individuals in clinical Stage 4 or Stage 5 of the Alzheimer's continuum.[5]

4. The subject and/or study partner report a gradual and progressive change in memory for ≥ 6 months.

5. Evidence for AD pathophysiology, confirmed either prior to or during the screening period prior to randomization, as follows:

    a. Prior to screening, confirmed with appropriate documentation by either: 1) CSF total tau/$A\beta_{42}$ ratio (must be ≥ 0.28), or 2) an abnormal amyloid or tau positron emission tomography (PET) scan consistent with AD; or

    b. During screening, subjects must demonstrate an elevated plasma P-tau181 level (a research biomarker that identifies AD pathophysiology with high accuracy; see lab manual for details).

6. MMSE score ≥ 16 and ≤ 27 at screening.

7. CDR-GS must be 0.5, 1 or 2.

8. If female, either surgically sterile or postmenopausal for at least 1 year.

9. Male subjects must be willing to use contraception during the study. With female partners of childbearing potential, male subjects, regardless of their fertility status, must agree to either remain abstinent or use condoms in combination with one additional highly effective method of contraception (e.g., oral or implanted contraceptives, or intrauterine devices) or an effective method of contraception (e.g., diaphragms with spermicide or cervical sponges) during the study and for 14 days after study drug dosing has been completed.

10. Fluency in a language of the research site and the utilized assessment materials.

11. Has adequate visual and auditory acuity (in the Investigator's judgment) that is sufficient to complete all scheduled assessments (eyeglasses and hearing aids are permitted).

12. If receiving background AD medications, including cholinesterase inhibitors, memantine, neuroleptics, antidepressants, anxiolytics, or sleep medications, the dosing regimen must be stable for at least 12 weeks prior to Study Day 1 (randomization) and should be expected to remain stable during the study (Note – barbiturates, meprobamate, and high dose benzodiazepines are not allowed, while low dose benzodiazepines, zolpidem, zaleplon and suvorexant are permitted).

13. The subject has not been a smoker or chewed tobacco for at least 3 years.

14. Availability of a person (a study partner) who, in the Investigator's opinion, has frequent and sufficient contact with the study subject (defined as ≥10 hours per week), and can:

    a. provide accurate information regarding the study subject's cognitive and functional abilities,

    b. agree to comply with and participate at all scheduled visits and study procedures,

    c. sign the necessary consent form,

    d. maintain the same level of interaction with the study subject throughout the study duration.

15. Individuals who have participated in a clinical study with an investigational drug targeting the underlying AD process are permitted to participate in this study on a case-by-case basis after consultation between the Principal Investigator and the Sponsor (subjects known to have been randomized to placebo do not require such consultation

and are permitted to participate).

5.3. EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

1. Residence in a skilled nursing facility requiring 24-hour care (Note – subjects may reside in an assisted living facility if they do not need 24-hour care).

2. Any contraindications to study procedures (e.g., potential subjects with a pacemaker must be excluded due to the required MRI during screening).

3. A medical condition or treatment with an anticoagulant that would interfere with a lumbar puncture for those subjects being considered for participation in the CSF biomarker assessment.

4. BMI < 18.5 or > 35.0

5. Evidence of a neurologic condition other than AD that, in the judgment of the Investigator, significantly contributes to the subject's dementia, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, Huntington's disease, or normal pressure hydrocephalus.

6. Subjects with any current primary psychiatric diagnosis other than AD if, in the judgment of the Investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the subject's ability either to comply with study procedures or to complete the study. Patients with a history of schizophrenia or chronic psychosis are excluded.

7. Geriatric Depression Scale (15-item) score > 8.

8. Affirms suicidal ideation in response to questions number 4 or 5 in the C-SSRS during the past 3 months (i.e., "active suicidal ideation with some intent to act, without specific plan," or "active suicidal ideation with specific plan and intent") or affirms any of the questions contained in the Suicidal Behavior section of the C-SSRS as applicable during the past 12 months.

9. Meets DSM-V criteria for alcohol or substance use disorder within 2 years before the Screening Period.

10. MRI presence of cerebral vascular pathology (including, but not limited to, hemorrhage, infarct > 1 cm^3, or > 3 lacunar infarcts), cerebral contusion, symptomatic

subdural hematoma, aneurysm, or space-occupying lesion deemed clinically significant in the opinion of the Investigator.

11. History of transient ischemic attack (TIA) or stroke within 12 months of screening, or history of a stroke concurrent with the onset of dementia.

12. History of seizure within 12 months of screening.

13. History of severe head trauma; history of head trauma with loss of consciousness > 10 min within 12 months of screening; history of head trauma concurrent with the onset of dementia; history of head trauma likely to be contributing to the subject's cognitive impairment in the Investigator's judgment.

14. Onset of dementia secondary to cardiac arrest, surgery with general anesthesia, or resuscitation.

15. Clinically significant, untreated or inadequately treated sleep apnea that is likely to be contributing to the subject's cognitive impairment in the Investigator's judgment.

16. Insufficiently controlled diabetes mellitus, defined as:

    a. requiring insulin treatment (unless subject has been stable for at least 4 weeks prior to screening on a once-daily dose of long-acting insulin), or

    b. HbA1C > 8.0% during the Screening Period.

17. Malignant tumor within 3 years before screening (except definitively treated squamous or basal cell carcinoma, cervical carcinoma in situ, localized non-progressive prostate cancer, localized stage 1 bladder cancer or colon polyp resolved by excision, per judgment of the Investigator).

18. Known positive HIV status.

19. Positive HBsAg or HCV-Ab during screen.

20. Positive urine drug screen for substances of abuse.

21. Vitamin B12 level lower than the normal limit at the time of screening (and that remains below on repeat testing). Subjects may be enrolled following initiation of B12 therapy for at least 4 weeks prior to randomization with confirmation of a normal level upon repeat testing.

22. Thyroid-stimulating hormone (TSH) levels greater than the upper limit of normal and a free thyroxine (free T4) lower than the lower limit of normal; subjects on thyroid

supplementation for hypothyroidism must be on a stable dose for ≥ 3 months before screening.

23. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – subjects with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN).

24. History or diagnosis of clinically significant ischemic heart disease (e.g., myocardial infarction or unstable angina within 1 year of screening), moderate to severe congestive heart failure, cardiomyopathy, myocarditis or valvular heart disease of clinical significance in the Investigator's judgment.

25. History of or current clinically significant cardiac arrhythmia or heart block as evidenced by ECG in the judgment of the Investigator.

26. Clinically significant abnormality on screening electrocardiogram (ECG), including, but not necessarily limited to, a confirmed QT interval by the Fridericia correction formula (QTcF) > 470 msec (females) or > 450 msec (males) based on WHO 2016 guidelines.

27. Insufficiently controlled hypertension (defined, at rest, as systolic BP > 160 mmHg or diastolic BP > 100 mmHg; if an initial BP reading is elevated, an additional measurement during the Screening Period could be used before excluding a potential subject for insufficiently controlled hypertension).

28. Hypotension (systolic BP < 90 mmHg) or bradycardia with a heart rate less than 50 beats per minute during screening (out of range values may be repeated once for confirmation).

29. Use of medications that in the Investigator's opinion will contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or other study procedures.

30. Donepezil > 10 mg/day, currently or within 12 weeks of Study Day 1 (randomization).

31. Discontinued AChEI < 12 weeks prior to randomization.

32. Administration of aducanumab, either currently or previously prescribed (Note – administration of aducanumab at any point during this clinical study is prohibited).

33. Antipsychotics (Note – low doses are allowed only if given for sleep disturbances,

agitation, aggression or dementia-related psychosis, and only if the dose has been stable for at least 4 weeks prior to screening).

34. Tricyclic antidepressants and monoamine oxidase inhibitors if prescribed within 4 weeks prior to screening; all other antidepressants are allowed only if the dose has been stable for at least 4 weeks prior to screening.

35. Immunosuppressants, including systemic corticosteroids, if taken in clinically immunosuppressive doses (steroid use for allergy or inflammation is permitted).

36. Use of antiepileptic medications if taken for control of seizures (Note – use of antiepileptic medications are allowed if used for mood stabilization).

37. Chronic intake of opioid-containing analgesics.

38. Use of prescribed sedating H1 antihistamines.

39. Use of nicotine therapy (all dosage forms including a patch), varenicline (Chantix), or similar therapeutic agent within 4 weeks prior to screening.

40. Loss of a significant volume of blood (> 450 mL) within 4 weeks of randomization.

41. COVID-19 infection within 3 months of screening (Note – the subject must be fully vaccinated for COVID-19 at least two weeks prior to Study Day 1 [randomization] if there is no history of a prior COVID-19 infection).

42. Clinically significant abnormalities on screening laboratory tests in the judgment of the Investigator.

43. Unstable medical condition that is clinically significant in the judgment of the Investigator, including significant neurologic, hepatic, renal, endocrinologic, cardiovascular, gastrointestinal, pulmonary, hematologic, immunologic or metabolic disease.

44. Any other medical or neurological condition (other than Alzheimer's disease), that, in the opinion of the Investigator, might represent a contributing cause to the subject's cognitive impairment, or affect cognitive assessment, subject safety, ability to comply with study assessments, drug compliance and completion of the study.

6. STUDY DRUG

6.1. SIMUFILAM PHYSICAL DESCRIPTION AND PREPARATION

Investigational simufilam and matching placebo will be supplied by Cassava as coated tablets including 50 and 100 milligram active strengths.

All remaining unused simufilam study drug will be returned to the Sponsor or designee.

6.1.1 Packaging and Labeling

Simufilam or placebo tablets in plastic bottles will be supplied in 70-count bottles for a 4-week supply or 188-count bottles for a 12-week supply. Bottles include a desiccant canister and are closed with a foil seal and child-resistant (CR) cap. Each bottle contains 7 or 10 days of extra medication to accommodate scheduling flexibility with clinic visits.

A Medication Event Monitoring System (MEMS®) that is 21 CFR Part 11 compliant will be used to track adherence to the b.i.d. dosing schedule. CR-MEMS® caps will be supplied to replace the conventional CR cap on each bottle. One (1) CR-MEMS cap will be assigned to each subject for use throughout the study. Each CR-MEMS cap has an LCD display that provides immediate visual indication of the number of doses taken that day and the number of hours since the prior dose that day, resetting to zero each night. Instructions on management and use of CR-MEMS caps will be provided in the Pharmacy manual and during site training.

Each bottle is labeled with a unique double-blind ID number that is randomly assigned to a treatment. A computer-based clinical study management system will specify the bottle ID number to be dispensed according to the subject's treatment randomization.

6.1.2 Storage

The investigational drug supplies must be stored in a locked cabinet or room with limited access at controlled room temperature, 20-25º C (68-77º F) and protected from moisture.

6.1.3 Drug Accountability

The Investigator will be responsible for monitoring the receipt, storage, dispensing and accounting of all study medications according to site standard operating procedures (SOPs). All records documenting the chain of custody for the study medication must be retained in the site study file. Accurate, original site records must be maintained of drug inventory and dispensing. All records must be made available to the Sponsor (or designee) and appropriate regulatory agencies upon request.

6.2. ADMINISTRATION AND DOSING REGIMEN

Subjects will be randomized to receive placebo, or 50 mg or 100 mg simufilam b.i.d. (approximately 361 subjects per treatment group). Study drug should be taken at least 1 h before or after a meal.

6.3. CONCOMITANT MEDICATIONS

Use of prescription or non-prescription medications will be recorded during the study. Chronic medications must be stable for 4 weeks prior to screening [Note – see Inclusion Criterion #12 and Exclusion Criteria #30 and #31 for additional details regarding background medications frequently prescribed to patients with AD].

7. STUDY PROCEDURES

Appendix A presents the Schedule of Activities.

Prior to any study-related activities, the Informed Consent Form (ICF) must be signed and dated by the subject (or a legally authorized representative) and the study partner. The format and content of the ICF must be agreed upon by the Principal Investigator(s), the appropriate IRB and the Sponsor. The signed and dated ICF must be retained by the Investigator in the subject's file.

7.1. EVALUATIONS BY VISIT

Follow-up visits can be scheduled ± five (5) days from the targeted Study Visit date.

7.1.1. Screening Period (No greater than a 60-day duration prior to Study Day 1)

The Sponsor recognizes the Screening Period assessments and procedures may not necessarily be completed in a single visit. A subject is permitted to be screened over more than one calendar day if, in the Investigator's judgment, such scheduling will optimize the accuracy of Screening Period assessments and procedures. The following will be completed during the Screening Period:

- Informed Consent.
- Review of Inclusion and Exclusion Criteria
- Collect demographic information (e.g., sex, date of birth, race/ethnicity, years of education)
- Medical and surgical history

- Review concomitant medications, and any discontinued medications, in the 4 weeks prior to screening
- To the extent such information is available, review and record any investigational drugs administered during past clinical study participation regardless of the date of such participation
- History of drug, alcohol and tobacco use
- eCOA order of administration at screening:
  - MMSE
  - CDR
  - Geriatric Depression Scale
  - C-SSRS – Baseline/screening version
- Complete physical and neurologic examination; including measurement of key vital signs (blood pressure [supine], temperature, pulse rate), height and weight (to calculate BMI)
- A 12-lead ECG (5-min supine)
- Laboratory assessments, including: routine serum chemistry, TSH, free T4, Vitamin B12 levels, HBsAg, HCV-Ab, hematology, urinalysis and urine screen for drugs of abuse. Plasma for P-tau181 assessment will also be collected unless there is documented evidence of AD pathophysiology prior to screening.
- Once the clinical and laboratory assessments above have been completed and verified to be consistent with study participation, schedule brain MRI to confirm subject meets MRI-specific entry criteria (Note –previous brain MRI results, with appropriate documentation, will be accepted for up to 6 months prior to the Study Day 1 Visit unless a recent clinical event warrants a repeat scan).
  - Subjects participating in the MRI sub-study assessment of brain volume (150 total; 50 subjects/group), including the hippocampus, ventricles and whole brain, will have, in addition to the MRI during the Screening Period, subsequent MRI scans at Weeks 40 and 76.

7.1.2. Sub-studies with PET and fluid biomarkers

Selected research sites will participate in additional sub-study assessments to determine the effect of simufilam on anatomical and biomarker secondary endpoints.

- Subjects participating in either amyloid or tau PET sub-studies (40 and 50 subjects/group, respectively) will be scheduled for their first PET scan prior to Study Day 1; they will undergo the procedure again at Week 76. Individual subjects can potentially participate in both PET imaging sub-studies, but consideration must be given to total radiation exposure based on the number of PET scans and dose each subject would receive per annum. Moreover, PET scans using different tracers must also be acquired at least 24 hours apart to ensure adequate wash-out of the previous tracer prior to new tracer administration.
- Subjects participating in the PET sub-studies will also have blood samples drawn for assessments of plasma-based biomarkers during the Screening Period and again at Weeks 28, 52 and 76 (≈ 270 total; ≈ 90 subjects/group). Subjects participating in the tau PET sub-study will also provide a plasma sample for PK at Weeks 28 and 76.
- Subjects participating in an assessment of CSF biomarkers (90 total; 30 subjects/group) will undergo lumbar puncture prior to Study Day 1 and again at Week 76.

7.1.3. Rescreening of a Subject

Individuals who have given informed consent and fail to meet the Inclusion and/or Exclusion criteria (screen failure) may not be rescreened if the screen failure is due to non-eligible MMSE (<16), MRI or P-tau181 results. If screen failure occurs for the following reasons, the subject is allowed one rescreen:

- Low vitamin B12 requiring supplemental therapy (can rescreen after 4 weeks)
- MMSE of 28 (can rescreen after 8 weeks)

Other reasons for screen failure will require Sponsor approval to rescreen.

7.1.4. Study Day 1 (Dosing Initiation)

Subjects will come to the clinic in the morning. Prior to dosing, the following assessments will be conducted:

- Confirmation of Inclusion/Exclusion criteria
- Confirm subject has been fully vaccinated for COVID-19 for at least two weeks if there is no history of a prior COVID-19 infection

- Review of concomitant medications
- Adverse Event Monitoring
- Vital signs (blood pressure [supine], temperature, pulse).
- Weight
- Brief physical and neurologic examination (Note: the brief physical and neurologic examination performed on Study Day 1 and at all subsequent visits will include an assessment of the following: general appearance; cardiovascular, pulmonary, and abdominal examination, as well as an examination of any other system in response to subject-reported symptoms; cranial nerves [II-XII], tone, power, deep tendon reflexes, coordination and gait)
- eCOA order of administration:
  - ADAS-Cog12
  - ADCS-ADL
  - NPI
  - ZBI
  - C-SSRS – Since Last Visit version
- ECG
- Clinical laboratory tests (blood and urine)
- Genotyping for ApoE

Once all Study Day 1 procedures and assessments have been completed, the subject is randomized to a treatment and the bottle of Study Drug to be dispensed is assigned by the computer-based study management system. A child-resistant Medication Event Monitoring System (CR-MEMS®) cap is drawn from stock for permanent assignment to the subject and initialized via the computer interface. Before removing Study Drug from the bottle, remove the original closure and apply the CR-MEMS cap as a replacement. Just prior to administering the first dose of Study Drug, remove the CR-MEMS cap and remove one (1) tablet.

Subjects will be administered Study Drug at least 1 hour before leaving the clinic and at least 1 hour before or after a meal. The subject will be discharged with their supply of Study Drug. The study partner will be trained on the features and proper use of the CR-MEMS cap and instructed to administer Study Drug twice daily at least 1 h before or after

a meal. The study partner should be advised that a dose can be up to 4 h late, but, if a dose is missed, the next dose should NOT be doubled.

Information and instruction for the computer-based study management system, and the CR-MEMS cap will be covered during site training, and written reference information will be included in the pharmacy manual.

For all follow-up visits, subjects will be instructed to come to the clinic in the morning and to bring their Study Drug bottle to the clinic. At each visit, the CR-MEMS cap will be read into the computer-based study management system to inform the site about the subject's Study Drug adherence. The CR-MEMS cap will be removed from the returned bottle and applied to the newly dispensed bottle of Study Drug.

7.1.5. Weeks 4, 16, 40 and 64 Follow-up Visits

Subjects will return to clinic for these scheduled visits within a ± 5-day "window."

- Vital signs (blood pressure [supine], temperature and pulse)
- Weight
- Brief physical and neurologic examination
- Adverse event monitoring
- Use of concomitant medications
- eCOA order of administration:
  - ADAS-Cog12 (whenever possible, within 1 h of the time of day administered at the Study Day 1 Visit, and by the same rater)
  - ADCS-ADL
  - ZBI
  - C-SSRS – Since Last Visit version
- Clinical laboratory tests (blood and urine)
- Weeks 4 and 40 only: resting ECG
- Week 40 only: for those 150 subjects participating in the MRI sub-study to determine the effect of simufilam on brain volume, schedule their Week 40 scan.

7.1.6. Weeks 28 and 52 Follow-up Visit

Subjects will return to clinic for these scheduled visits within a ± 5-day "window."

- Vital signs (blood pressure [supine], temperature and pulse)
- Weight
- Brief physical and neurologic examination
- Adverse event monitoring
- Use of concomitant medications
- eCOA order of administration:
  - ADAS-Cog12 (whenever possible, within 1 h of the time of day administered at the Study Day 1 Visit, and by the same rater)
  - ADCS-ADL
  - MMSE
  - NPI
  - ZBI
  - C-SSRS – Since Last Visit version
- Clinical laboratory tests (blood and urine)
- For those 270 subjects participating in the amyloid or tau PET and plasma biomarker sub-studies, collect their Week 28 and Week 52 blood samples (including PK at Week 28 for those in the tau PET sub-study)

7.1.7. Week 76 End-of-Treatment Visit / Early Termination (ET) Visit

Subjects will return to clinic for this scheduled visit within a ± 5-day "window."

- Vital signs (blood pressure [supine], temperature and pulse)
- Weight
- Brief physical and neurologic examination
- Adverse Event monitoring
- Use of concomitant medications

- eCOA order of administration:
    - ADAS-Cog12 (whenever possible, within 1 h of the time of day administered at the Study Day 1 Visit, and by the same rater)
    - ADCS-ADL
    - MMSE
    - CDR
    - NPI
    - ZBI
    - C-SSRS – Since Last Visit version
- Resting ECG
- Clinical laboratory tests (blood and urine)
- For those 270 subjects participating in the amyloid or tau PET and plasma biomarker sub-studies, collect their Week 76 blood samples (including PK samples for those in the tau PET sub-study) and schedule their Week 76 scan.
- For those 150 subjects participating in the MRI sub-study to determine the effect of simufilam on brain volume, schedule their Week 76 scan.
- For those 90 subjects participating in the CSF biomarker sub-study, perform a lumbar puncture to collect CSF (5 mL) after all other testing has been completed.

Note: Early Termination subjects do not need to complete the electronic Clinical Outcome Assessments if performed within 30 days of the ET Visit (see Section 9 – Early Discontinuation)

7.1.8. Week 77-78 End-of-Study Follow-up

The subject will receive a follow-up phone call 7-14 days after the last dose for adverse event monitoring. If needed, a follow-up clinic visit will be scheduled.

7.1.9. Treatment after Study Completion

The Sponsor plans to initiate an open-label extension study for subjects who have completed participation in Study PTI-125-06. Should a subject elect to participate in the

open-label extension study, the End-of-Study Follow-up (Section 7.1.8) will not be conducted.

7.1.10. Unscheduled Visits and Discontinuation due to AEs

For unscheduled visits due to AEs, any assessments conducted will be at the discretion of the Investigator and pertinent to the AE. If a decision is made to discontinue the subject from study drug, the Sponsor will be notified immediately. The subject should be followed and treated by the Investigator until the AE has resolved or stabilized (see Section 10.1 – Adverse Events). Restarting the subject on study drug will be a mutual decision by the Investigator and the Sponsor. See also Section 9.0 – Early Discontinuation.

7.1.11. Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to ensure subject safety and to evaluate liver event etiology during administration of study drug. Potential discontinuation of study drug for abnormal liver function tests should be considered by the Investigator in consultation with the designated medical monitor if the study subject meets one or more of the following criteria:

- ALT or AST ≥ 4x ULN;
- ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN;
- ALT or AST ≥ 3x ULN if associated with the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia; or
- ALP elevations, if deemed of liver origin and drug-related as follows:
    - ALP > 3x ULN;
    - ALP > 2.5x ULN and total bilirubin > 2x ULN; or
    - ALP > 2.5x ULN if associated with the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia.

In the event of discontinuation due to abnormal liver function tests, the subject will be appropriately investigated to determine the potential cause and referred to a physician experienced in the treatment of hepatic disorders.

Study drug should be discontinued if a subject: (1) positively affirms suicidal ideation in response to questions number 4 or 5 in the Suicidal Ideation section of the C-SSRS, or (2) reports any suicidal behavior or non-suicidal self-injurious behavior since their last visit in response to the C-SSRS Suicidal Behavior questions.

Bodyweight loss of ≥ 2 kg resulting in a BMI < 18.5 is an additional stopping criterion.

7.2. LABORATORY ASSESSMENTS

7.2.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed during the Screening Period, Study Day 1 pre-dose, and at all follow-up visits:

- Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count.
- Serum Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphate, blood urea nitrogen (BUN), total bilirubin, creatinine, albumin, globulin, total protein, uric acid, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), lactose dehydrogenase (LDH).
- Urinalysis: color, specific gravity, pH, protein, glucose, ketones and occult blood.
- Screening Period: During the Screening Period only, bloods will be drawn for TSH, free T4, Vitamin B12, HepBsAg, HCV-Ab and plasma P-tau181 (Note – plasma collection for P-tau181 not required if subject has documented evidence of AD pathophysiology prior to screening). Urine to screen for drugs of abuse (amphetamines, cocaine, opiates and phencyclindine) will also be collected during the Screening Period.

7.2.2. Collection of Whole Blood Samples for ApoE Genotyping

Whole blood samples for genotyping ApoE will be collected on Study Day 1 (please review instructions as per lab manual).

7.2.3. Preparation of Plasma Biomarker and PK Samples from PET Sub-study Participants

At each blood collection for biomarkers and PK, blood samples will be drawn into two Vacutainer® tubes (10 mL per tube) containing K2EDTA. The tubes will be placed on ice. Within 30 min of collection, the blood will be centrifuged at approximately 1000 X G for 15 min, preferably at 4-5°C. Within 30 min of centrifuging, plasma will be transferred to polypropylene tubes and stored at -70°C until shipped to the central lab (complete instructions as per lab manual).

7.2.4. CSF assays

CSF samples should be split, with approximately 2.5 mL shipped to the central lab (as instructed per lab manual). The remaining CSF will be retained at the study site and frozen at -70°C or below until instructions are received from the Sponsor.

CSF samples will be collected during the Screening Period and again at Week 76 for those subjects participating in the CSF biomarker sub-study. The biomarkers to be assayed will include:

- Total Tau
- P-tau181
- Neurogranin
- sTREM2
- Amyloid-beta 42
- Neurofilament light chain

8. COGNITIVE AND FUNCTIONAL ASSESSMENTS

8.1. MINI-MENTAL STATE EXAM (MMSE)

The MMSE[6] is a set of standardized questions covering several target areas: orientation, registration, attention and calculation, short-term verbal recall, naming, repetition, 3-step command, reading, writing, and visuospatial cognitive assessment. Administration of the MMSE is estimated to take approximately 10 minutes.

8.2. CLINICAL DEMENTIA RATING (CDR)

Washington University's CDR[7] characterizes six domains of cognitive and functional performance applicable to AD and related dementias: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The study partner is interviewed first by a qualified rater who assesses all six domains. The subject is then interviewed in the absence of the caregiver. A CDR global score can be calculated by accessing Washington University's online algorithm (https://biostat.wustl.edu/~adrc/cdrpgm/index.html) where 0 = no dementia, and scores of 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively. The sum of boxes (i.e., CDR-SB)[8] can also be calculated by summing the six individual domain scores. This detailed quantitative general index may provide more information than the CDR-GS in patients with mild dementia.

8.3. ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE SUBSCALE 12 (ADAS-COG12)

The ADAS-Cog[9,10] is a psychometrician-administered battery comprised of several cognitive domains including memory, comprehension, praxis, orientation, and spontaneous speech. The ADAS-Cog12 (which includes Delayed Word Recall) will be administered to all subjects at various key visits throughout the study.

8.4. NEUROPSYCHIATRIC INVENTORY (NPI)

A study partner interview, the 12-item NPI[11] records frequency and severity of common neuropsychiatric symptoms in dementia (Hallucinations, Delusions, Agitation/aggression, Dysphoria/depression, Anxiety, Irritability, Disinhibition, Euphoria, Apathy, Aberrant motor behavior, Sleep and nighttime behavior change, Appetite and eating change). The study partner is then asked to rate their own distress for the subject's behavioral symptoms occurring in the past 4 weeks.

8.5. ALZHEIMER'S DISEASE COOPERATIVE STUDY – ACTIVITIES OF DAILY LIVING (ADCS-ADL-AD)

The ADCS-ADL[12] is a 23-item study partner questionnaire that covers both basic activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal).

8.6. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

The C-SSRS[13] is an assessment tool used to assess the lifetime suicidality of a subject (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit).

8.7. ZARIT BURDEN INTERVIEW (ZBI)

The ZBI[14,15] is a 22-item scale designed to assess the stress or burden experienced by caregivers of people with dementia. The ZBI will be administered as an interview with the caregiver. The scale consists of 22 statements reflecting how people can feel when taking care of another person. The statements are phrased as questions for the caregiver to indicate how often they feel the way described in the statement. The 5 possible responses for each item are Never, Rarely, Sometimes, Quite Frequently, and Nearly Always.

8.8. GERIATRIC DEPRESSION SCALE (GDS)

The GDS[16] is a 30-item yes/no question test designed to screen for depression in elderly

persons. The GDS short form (15-items)[17] version utilized in this study will be clinician administered with caregiver input. Subjects will be evaluated for symptoms of depression during the Screening Period.

8.9. ELECTRONIC CAPTURE OF RATING SCALES

The assessments MMSE, CDR, ADAS-Cog12, GDS, NPI, ADCS-ADL, C-SSRS, and ZBI will be captured electronically by an eCOA platform that is 21 CFR Part 11 compliant. Data collected by eCOA will be transferred directly to the EDC vendor's database.

9. EARLY DISCONTINUATION

Subjects may choose to discontinue study drug or study participation at any time, for any reason, and without prejudice. Moreover, a subject may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral or administrative reasons. Discontinued subjects should be followed according to medical practice standards, and the outcome documented. Follow-up is required if the subject is discontinued due to an adverse event (AE). Any comments (spontaneous or elicited) or complaints made by the subject and the reason for termination and the date of stopping the drug must be recorded in the Case Report Form (CRF) and source documents.

The following must be completed and documented in the source documents and CRFs for all subjects who discontinue the study early:

- The reason for early study discontinuation. If the subject is withdrawn for more than one reason, each reason should be documented in the source documents and the most clinically relevant reason should be entered on the CRF.
- Vital signs (blood pressure, temperature and pulse), brief physical and neurologic examination, weight, clinical laboratory tests, ECG, use of concomitant medications and adverse events should be obtained at discharge prior to release.
- Blood draw for plasma biomarkers
- ADAS-Cog, MMSE, CDR, ADCS-ADL, NPI, ZBI and C-SSRS (as detailed in Section 7.1.7 – Early Termination Visit), if not performed within the last 30 days.

10. ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

10.1. ADVERSE EVENTS - DEFINITION

An Adverse Event (AE) is any undesirable event that occurs to a subject during a study, whether or not that event is considered study drug-related. Monitoring for AEs will start at dosing. Examples include:

- Any treatment-emergent signs and symptoms (events that are marked by a change from the subject's baseline/entry status [e.g., an increase in severity or frequency of pre-existing abnormality or disorder])
- All reactions from study drug, an overdose, abuse of drug, withdrawal phenomena, sensitivity or toxicity to study drug
- Apparently unrelated illnesses
- Injury or accidents (Note: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate medical events [e.g., for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately])
- Extensions or exacerbations of symptoms, subjective subject-reported events, new clinically significant abnormalities in clinical laboratory, physiological testing or physical examination

All AEs, whether or not related to the study drug, must be fully and completely documented on the AE page of the CRF and in the subject's clinical chart.

In the event that a subject is withdrawn from the study because of an AE, it must be recorded on the CRF as such. The subject should be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

The Investigator must report all directly observed AEs and all spontaneously reported AEs. The Investigator will ask the subject a non-specific question (e.g., "Have you noticed anything different since your dose of the study medication?") to assess whether any AEs have been experienced since the last assessment. AEs will be identified and documented in the Electronic Data Capture (EDC) system in appropriate medical terminology. The severity and the relationship to the study drug will be determined and reported in EDC (see below).

10.2. ADVERSE EVENTS - SEVERITY RATING

The severity of each AE should be characterized and then classified into one of three clearly defined categories as follows:

- Mild – the AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.
- Moderate – the AE produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment.
- Severe – the AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

These three categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's report and the physician's observations. The severity of the AE should be recorded in the appropriate section of the EDC.

10.3. ADVERSE EVENTS – RELATIONSHIP TO STUDY DRUG

The relationship of each AE to the study drug will be classified into one of three defined categories as follows:

- Unlikely – a causal relationship between the AE and the study drug is unlikely.
- Possible – a causal relationship between the AE and the study drug is possible.
- Probable – a causal relationship between the AE and the study drug is probable. For example, the AE is a common adverse event known to occur with the pharmacological class of the study drug; or the AE abated on study drug discontinuation and reappeared upon rechallenge with the study drug.

These three categories are based on the Investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's report, the timing of the AE in relationship to study drug administration/discontinuation, the physician's observations and the physician's prior experience. The relationship of the AE to the study drug will be recorded in the appropriate section of the EDC.

10.4. SERIOUS ADVERSE EVENTS AND UNEXPECTED ADVERSE EVENTS - DEFINITIONS

A Serious Adverse Event (SAE) includes (but is not limited to) an experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (i.e., the subject is at immediate risk of death from the reaction as it occurs). "Life-threatening" does not include an event that, had it occurred in a more serious form, might have caused death. For example, drug- induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
- In-patient hospitalization (hospital admission, not an emergency room visit) or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity (i.e., a substantial disruption of the subject's ability to carry out normal life functions).
- A congenital anomaly/birth defect.

In addition, medical and scientific judgment should be exercised in deciding whether other situations should be considered an SAE (i.e., important medical events that may not be immediately life-threatening or result in death but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above). Examples of such medical events include (but are not limited to): allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

An **unexpected** AE is one for which the specificity or severity is not consistent with the current Investigator's Brochure. For example, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure listed only elevated hepatic enzymes or hepatitis.

Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

10.5. SERIOUS ADVERSE EVENTS REPORTING

The reporting of SAEs by the Sponsor to regulatory authorities (e.g., FDA) is a regulatory requirement. Each regulatory agency has established a timetable for reporting SAEs based upon established criteria. Likewise, it is the responsibility of the Principal Investigator to report SAEs to the IRB.

All SAEs must be reported immediately **(within 24 h of learning of the event)** by e-mail to:

Premier Research Global Pharmacovigilance
[redacted]

Do not delay reporting a suspected SAE to obtain additional information. Any additional information, if collected, can be reported to the Sponsor as a follow-up to the initial report.

SAEs must be immediately reported to the responsible IRB.

In the case of a death or other SAE that has occurred within 30 days after receiving study drug, the Principal Investigator must also report such an event within 24 hours of being notified. Your local IRB may also require these reports.

In the event of any SAE (other than death), the subject will be instructed to contact the study physician (Principal Investigator or designee) using the phone number provided in the Informed Consent Form. All subjects experiencing an SAE will be seen by a Principal Investigator or designee as soon as feasible following the report of an SAE.

11. STATISTICAL CONSIDERATIONS

11.1. RANDOMIZATION

Randomized treatments will be assigned by subject numbers in a randomly generated numeric sequence.

The randomization code will not be revealed to study subjects, Investigators, clinical staff, study monitors or the Sponsor until all subjects have completed therapy and the database has been finalized and locked.

Under normal circumstances, the blind should not be broken. The blind may be broken only if specific emergency treatment is indicated. The date, time and reason for the unblinding must be documented in the CRFs, and the medical monitor must be informed as soon as possible.

11.2. ANALYSIS POPULATIONS

The Intent-To-Treat (ITT) analysis set includes all randomized subjects. All efficacy analyses will be conducted in this analysis set and subjects will be included in the group to which they were randomized.

The Safety analysis set includes all subjects who receive study treatment. All safety analyses will be completed in the Safety analysis set and subjects will be included in the group based on the treatment actually received.

11.3. STATISTICAL ANALYSIS

11.3.1. Primary Efficacy Analysis

Each of the two co-primary endpoints will be analyzed using a linear mixed model for repeated measurements. The dependent variable is the change from baseline and the model will include fixed effects for treatment group (three levels), week (7 levels, corresponding to Weeks 4, 16, 28, 40, 52, 64 and 76), the treatment group-by-week interaction, and the randomization stratification variable. The baseline value of the corresponding endpoint will be included as a covariate and the unstructured covariance model will be used. The Study Day 1 ADAS-Cog12 and ADCS-ADL assessments will represent the baseline value for these variables.

For each of the two co-primary endpoints, the primary analysis will compare the 100 mg group and the placebo group at Week 76 using a two-sided test at the alpha = 0.05 level of significance. Study success requires that both co-primary comparisons are statistically significant.

11.3.2 Key Secondary Analysis

If both primary comparisons are statistically significant, then the corresponding comparisons at Week 76 for the 50 mg group versus the placebo group will be tested at the alpha = 0.05 level of significance (two-sided).

11.3.3 Other Secondary Analyses

The iADRS[18,19] is a linear combination of scores from two well-established, widely accepted, therapeutically sensitive measures of AD: the ADAS-Cog and ADCS-iADL (the instrumental component of the ADCS-ADL). The iADRS has been validated and statistical properties of the composite performance have been described[20]. All items of the ADAS-Cog12 and the ADCS-iADL will be included to generate this primary efficacy composite measurement without additional weighting.

Secondary clinical endpoint data (iADRS, NPI, MMSE and ZBI) measured repeatedly will be analyzed by linear mixed models for repeated measurements, as described above for the primary analysis.

Plasma assays may include P-tau181, SavaDx, neurofilament light chain and other biomarkers. All plasma biomarker data and MRI data measured repeatedly will be analyzed

by linear mixed models for repeated measurements, as described above for the primary analysis.

CSF biomarker endpoints to be analyzed include: 1) neurogranin, 2) neurofilament light chain, 3) total tau, 4) P-tau181, 5) sTREM2, and 6) $A\beta_{42}$. Additional CSF biomarkers may be measured. All CSF biomarker data, PET imaging data and CDR-SB will be analyzed using ANCOVA models with treatment group as a factor and the baseline value of the corresponding endpoint as a covariate.

All secondary analyses will be conducted using two-sided tests at the alpha = 0.05 level of significance, with no adjustments for multiplicity.

11.4. Safety Analysis

Adverse events reported on case report forms will be mapped to preferred terms and organ systems using the MedDRA mapping system. Vital signs and clinical laboratory results will be descriptively summarized in terms of change from screening values.

11.5. Sample Size

Approximately 1,083 subjects will be enrolled in this study. The sample size was determined by a power analysis of ADAS-Cog in a similar population over 76 weeks. This analysis determined that the comparison between an active arm and placebo requires group sizes of 289 to provide 90% power to detect a 45% difference from placebo at 76 weeks, based on the use of a two-sided test at the alpha = 0.05 significance level. The power calculation assumes a true mean change from baseline for placebo of 6.0 points and a standard deviation of 10.0 points. Assuming a drop-out of 20%, each treatment group should enroll 361 subjects.

12. STUDY TERMINATION

The study will be terminated following completion of the study or at any time at the discretion of the Sponsor.

13. DATA COLLECTION, RETENTION AND MONITORING

13.1. Case Report Forms

The CRF will be provided as an Electronic Data Capture (EDC) system that will serve as the collection method for subject data. The subjects in the study will not be identified by

name on any study documents to be collected by the Sponsor (or CRO designee) but will be identified by a unique subject number.

All clinical information requested in this protocol will be recorded in the EDC system. It is strongly recommended that data entry be completed within 48 h of a subject's visit. In case of error noted on paper source documents, the correction will be noted, initialed and dated.

EDC data must be reviewed and verified for accuracy and signed-off by the staff personnel before database lock. Paper source documents, if used, will remain at the Investigator's site at the completion of the study.

13.2. Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee) and Regulatory Agency (e.g., FDA) inspectors upon request. To assure accuracy of data collected in the EDC, it is mandatory that Sponsor representatives have access to original source documents (e.g., subject records, subject charts, and laboratory reports). During review of these documents, the subject's anonymity will be maintained with adherence to professional standards of confidentiality and applicable laws. A file for each subject must be maintained that includes the signed ICF and all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents for the EDC.

Investigators are required to maintain all study documentation until notification by the Sponsor that any records may be discarded.

The Investigator is responsible for maintaining adequate case histories in each subject's source records.

13.3. Subject Confidentiality

All reports and subject samples will be identified only by the assigned subject number and initials, as applicable by local law, to maintain subject confidentiality. Additional subject confidentiality measures (as required by region) will be covered within the Clinical Trial Agreement for each site as applicable.

13.4. Liability

In the event of a side effect or injury, appropriate medical care as determined by the Investigator or his/her designated alternate will be provided.

If a bodily injury is sustained resulting directly from the Study Drug, the Sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury that is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and his/her staff. No other compensation of any type will be provided by the Sponsor. Compensation for lost wages, disability or discomfort due to the study is not available.

13.5. Ethical and Legal Issues

The Investigator and site personnel are responsible for conducting this study in accordance with the ICH, GCP, and all other applicable laws and regulations.

13.5.1. Institutional Review Board

The protocol, ICF, clinical sites and Investigators must be approved by an IRB before the study is initiated. The IRB must comply with U.S. CFR 21 Part 56 and local laws.

Documentation of approval by the designated central IRB will be provided to the Investigators. The Sponsor will:

- Obtain IRB approval of the protocol, ICF, advertisements to recruit subjects and IRB approval of any protocol amendments and ICF revisions before implementing the changes.
- Provide the IRB with any required information before or during the study.
- Submit progress reports to the IRB, as required, requesting additional review and approval, as needed; and provide copies of all relevant IRB communications to the Investigator.

The Investigator is responsible for:

- Notifying the IRB within 15 calendar days of all SAEs and unexpected AEs related to study medications.
- Obtaining approval by their institution’s own IRB, if the Investigator’s institution has its own IRB.

13.6. Informed Consent Form

The Sponsor will submit the ICF to the central IRB for approval. An IRB-approved copy of the ICF will be forwarded to the Investigator or site staff.

The ICF documents study-specific information the Investigator provides to the subject

and the subject's agreement to participate. The Investigator explains in plain terms the nature of the study along with the aims, methods, anticipated benefits, potential risks, and any discomfort that participation may entail. The ICF must be signed and dated before the subject enters the study. The original ICF and any amended ICF, signed and dated, must be retained in the subject's file at the study site and a copy must be given to the subject.

14. INVESTIGATOR RESPONSIBILITIES

The Investigator agrees to:

- Conduct the study in accordance with the protocol, except to protect the safety, rights, or welfare of subjects.
- Personally conduct or supervise the study.
- Ensure that requirements for obtaining informed consent and IRB review and approval comply with ICH, CFR 21 Parts 50 and 56 and local laws.
- Report to the Sponsor any AEs that occur during the study in accordance with ICH, CFR 21 Part 312.64 and local laws.
- Read and understand the Investigator's Brochure including potential risks and side effects of the drug.
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate records in accordance with ICH, 21 CFR Part 312.62, and local laws and have records available for inspection by the Sponsor, FDA, or other authorized agency.
- Promptly report to the IRB and the Sponsor all changes in research activity and unanticipated problems involving risks to subjects or others (including amendments and expedited safety reports).
- Comply with all other requirements regarding obligations of Clinical Investigators and all other pertinent requirements listed in ICH, 21 CFR Part 312 and local laws.

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16. APPENDIX A – SCHEDULE OF ACTIVITIES

Procedures	Screening Period -60 Days to 0	Baseline Day 1	Week 4	Week 16	Week 28	Week 40	Week 52	Week 64	Week 76 ET/ED[7]	Week 77 to 78
Informed Consent	X									
I/E Criteria	X	X								
Medical & Med History	X									
Adverse Events		X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	
Physical Examination	X[1]	X	X	X	X	X	X	X	X	
Neurologic Examination	X[1]	X	X	X	X	X	X	X	X	
Height	X									
Weight	X	X	X	X	X	X	X	X	X	
Geriatric Depression Scale	X									
Resting ECG	X	X	X			X			X	
Biochemistry, Hematology, Urinalysis	X	X	X	X	X	X	X	X	X	
Urine Drug Screen	X									
TSH, free T4, B12, HBsAg, HCV-Ab	X									
Plasma P-tau181	X[12]									
Genotyping sample		X								
MRI	X					X[2]			X[2]	
Plasma Biomarkers	X[3]				X[3,11]		X[3]		X[3,11]	
CSF Biomarkers	X[4]								X[4]	
Amyloid PET	X[5]								X[5]	
Tau PET	X[6]								X[6]	
MMSE	X				X		X		X	
ADAS-Cog12		X	X	X	X	X	X	X	X	
ADCS-ADL		X	X	X	X	X	X	X	X	

Procedures	Screening Period -60 Days to 0	Baseline Day 1	Week 4	Week 16	Week 28	Week 40	Week 52	Week 64	Week 76 ET/ED[7]	Week 77 to 78
CDR	X								X	
NPI		X			X		X		X	
ZBI		X	X	X	X	X	X	X	X	
C-SSRS	X[8]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	
Drug Dispensation		X[10]	X	X	X	X	X	X		
Drug Accountability			X	X	X	X	X	X	X	
End of Study Follow-up Phone Call										X

1. Complete Physical and Neurologic Examinations during the Screening Period only, brief examinations thereafter
2. MRI sub-study subjects only (150 subjects total; 50 subjects/group)
3. Plasma biomarker sub-study subjects only; these are the same subjects in both PET sub-studies (270 subjects total; 90 subjects/group)
4. CSF biomarker sub-study subjects only (90 subjects total; 30 subjects/group)
5. Amyloid PET sub-study subjects only (120 subjects total; 40 subjects/group)
6. Tau PET sub-study subjects only (150 subjects total; 50 subjects/group)
7. Early Termination / Early Discontinuation subjects do not need to complete the electronic clinical outcome assessments if performed within 30 days of the ET/ED Visit
8. During the Screening Period, the C-SSRS Baseline/Screening version will be administered
9. At Study Day 1, as well as all remaining visits, the C-SSRS Since Last Visit version will be administered
10. The first dose of Study Drug is administered at the clinic
11. Plasma PK sample from tau PET sub-study participants
12. Plasma P-tau181 not required if the subject has evidence for AD pathophysiology prior to screening