7801 N. Capital of Texas Hwy, Ste. 260
Austin, TX 78731

CLINICAL RESEARCH PROTOCOL
PROTOCOL PTl-125-04

A 12-Month, Open-Label Safety Study of Simufilam followed by a 6-Month Randomized Withdrawal and 6 Additional Months Open-Label in Mild-to-moderate Alzheimer's Disease Patients

Sponsor:	**Cassava Sciences, Inc.** 7801 N. Capital of Texas Hwy, Ste. 260 Austin, TX 78731
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Protocol Date:	February 10, 2020
Amendment #1	March 17, 2020
Amendment #2	April 02, 2020
Amendment #3	May 6, 2020
Amendment #4	October 28, 2020
Amendment #5	December 30, 2020
Amendment #6	Feb 8, 2021
Amendment #7	**June 11, 2021**

This clinical trial is supported by NIH grant AG065152.

SUMMARY OF PROTOCOL AMENDMENT #7

Approvals:

Changed: Carrie Crowley
Director, Quality
Assurance

Changed to: Ben J. Murray
Sr. Clinical Project
Manager

Changed throughout where vital signs are listed:

- Vital signs (blood pressure, temperature, pulse and respiratory rate)

Changed to:

- Vital signs (blood pressure, temperature, pulse and respiratory rate), **and weight**

4. SUMMARY OF STUDY DESIGN

Changed: approximately 150 patients

Changed to: up to 200 patients

Added to list of Day 1 activities: and the C-SSRS.

Changed: PK blood samples will be obtained in the morning before dosing at all return visits except Months 4.5, 7.5 and 10.5.

Changed to: PK blood samples will be obtained in the morning before dosing at return visits on Months 15 and 18.

5.1 STUDY POPULATION

Changed: Between 100 and 150 patients will be enrolled

Changed to: Up to 200 patients will be enrolled

5.3 Exclusion Criteria

Changed 29, 30, 31, 32, 33: Prior to randomization

Changed to: Prior to enrollment

Changed 41: Loss of significant volume of blood (>450 mL) within 4 weeks prior to the study

Changed to: Loss of significant volume of blood (>450 mL) within 4 weeks prior to enrollment

Changed 42: COVID-19 infection within 3 months

Changed to: COVID-19 infection within 3 months of screening

7.2.1 *Screening Visit 1 (days -29 to 0)*

Added: Confirmation that the patient is either fully vaccinated for the COVID-19 virus at least 2 weeks prior to first dose of simufilam, or a positive serology test for the COVID-19 virus with no current symptoms

7.2.4 *Follow-up Visits on Months 1, 3, and 9, 13, 15 and 21*

Changed: Within 30 min prior to dosing, the following assessments will be conducted:

- Blood sample collection for PK assessment (for C_{min})

Changed to: Within 30 min prior to dosing, the following assessments will be conducted:

- Blood sample collection for PK assessment (for C_{min} – **Month 15 only**)

Changed: Cheek swab for genetic testing **Month 15 Visit only**

Changed to: Saliva collection for genetic testing **Month 15 Visit only**

7.2.5 *Follow-up Visit on Month 2*

Deleted: Blood sample collection for PK assessment (for C_{min})

7.2.6 *Follow-up Visits on Months 4.5, 7.5, and 10.5*

Changed: Patients will return to clinic at any time of day

Changed to: Patients will return to clinic at any time of day. The visit may be conducted by telemedicine, based on the judgement of the Investigator

7.2.7 *Follow-up Visit on Month 6 and 18*

Changed: Blood sample collection for PK assessment (for C_{min})

Changed to: Blood sample collection for PK assessment (for C_{min} – **Month 18 only**)

Moved from *After Dose* to *Within 30 min prior to dosing*: Plasma sample collection (from 8 mL whole blood) for SavaDx and other plasma biomarkers.

7.2.8 *Follow-up Visit on Month 12 and 24*

Added for clarity: Month 12 morning dose in the clinic will be from Open-Label Period 1 bottle. Month 12 evening dose will be from the Randomized Period 2 bottle.

Deleted: Blood sample collection for PK assessment (for C_{min})

Moved from *After Dose* to *Within 30 min prior to dosing*: Plasma sample collection (from 8 mL whole blood) for SavaDx and other plasma biomarkers.

7.3.2 *Preparation of Plasma Samples for Lymphocyte and Plasma Biomarker Determination*

Added: ***These patients with prior samples shipped as whole blood will continue to have samples shipped as whole blood only through Month 12. Samples at Months 15, 18, 21 and 24 will be spun to plasma.***

7.3.3 *Preparation of Plasma Samples for Pharmacokinetic Determination*

Changed: At each blood collection for PK (pre-dose samples for C_{min} at all visits except Months 4.5, 7.5 and 10.5),

Changed to: At each blood collection for PK (pre-dose samples for C_{min} at Months 15 and 18 only),

7.3.5 *Collection of Cheek Swab Saliva Samples for Genetic Testing*

Entire section changed from: Cheek swab saliva samples will be collected only at Month 15. Patients will refrain from eating or drinking 1 h prior to saliva collection. Each patient will be instructed to place a standard 2" × 2" piece of cotton gauze in the buccal region of their cheek for 3 min. The saliva-saturated cotton spit wad will be removed, rolled to fit a collection tube, and stored at -20°C until instructed to ship by the Sponsor.

Changed to: Saliva samples will be collected only at Month 15. Patients will refrain from eating or drinking 1 h prior to saliva collection. Each patient will be instructed to spit into a saliva collection tube. The saliva will be stored at -20°C until instructed to ship by the Sponsor.

8. EARLY DISCONTINUATION

Changed: Patients who discontinue will not be replaced.

Changed to: Patients who discontinue may be replaced at Sponsor discretion.

9.5 SERIOUS ADVERSE EVENTS REPORTING

Added: or notification via email through the EDC system

10.2 PHARMACOKINETIC ANALYSIS

Changed: The only plasma PK parameters to be collected from this study are the C_{min} values from blood samples taken prior to dosing on Months 1, 2, 3 and 9, as well as the sample on Month 6 or 12 collected just after the CSF draw (taken only if undergoing a CSF draw).

Changed to: The only plasma PK parameters to be collected from this study are the C_{min} values from blood samples taken prior to dosing at Months 15 and 18.

10.5 PHARMACOKINETIC ANALYSIS

Changed: Between 100 and 150 patients

Changed to: Up to 200 patients

15. APPENDIX A

Event schedule has been updated to reflect PK samples taken only at Months 15 and 18 and addition of weight when vital signs are taken. Modified footnote "a" to state patients should be reconsented at their next study visit. Additionally, a notation is made to omit drug dispensation at Month 24.

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

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Amendment #7

Approvals:

Lindsay H. Burns, PhD
SVP, Neuroscience
Cassava Sciences, Inc.

11 June 2021
Date

Nadav Friedmann, PhD, MD
Chief Operating and Medical Officer
Cassava Sciences, Inc.

6-11-2021
Date

Michael Marsman, PharmD
Regulatory Affairs Consultant
Cassava Sciences, Inc.

June 6-2021
Date

Ben J. Murray
Sr. Clinical Project Manager
Cassava Sciences, Inc.

11-JUN-2021
Date

Antonio Hernandez, PsyD
Executive Director, Clinical Research
Cassava Sciences, Inc.

11 JUN 2021
Date

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

A 12-Month, Open-Label Safety Study of Simufilam followed by a 6-Month Randomized Withdrawal and 6 Additional Months Open-Label in Mild-to-moderate Alzheimer's Disease Patients

Signature of Agreement for Protocol PTI-125-04
Amendment #7

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.

_____ _____

Principal Investigator Signature Date

_____

Print Principal Investigator Name and Title

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1. LIST OF ABBREVIATIONS

α7nAChR	α7 nicotinic acetylcholine receptor
$A\beta_{42}$	amyloid $beta_{1-42}$
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog11	Alzheimer's Disease Assessment Scale cognitive subscale 11
ADME	absorption, distribution, metabolism, excretion
ANDI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
C_{min}	minimum plasma concentration
C_{max}	maximum plasma concentration
CSF	cerebrospinal fluid
CSI	Cassava Sciences, Inc.
C-SSRS	Columbia-Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FDA	Federal Drug Association
FIH	first in human
FLNA	filamin A
GCP	good clinical practice
GDS	geriatric depression scale
GGT	gamma glutamyl transpeptidase
GLP	good laboratory practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hERG	human ether-a-go-go-related gene
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	Institutional Review Board

LDH	lactose dehydrogenase
LOQ	limit of quantitation
MI	myocardial infarction
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NMDAR	N-methyl D-aspartate receptor
NOAEL	no observable adverse effect level
NOEL	no observable effect level
NfL	neurofilament light chain
NPI	neuropsychiatric inventory
OTC	over-the-counter
PK	pharmacokinetics
PTI-125	small molecule drug candidate to treat AD
PTI-125Dx	blood-based diagnostic/biomarker candidate
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SOP	standard operating procedure
TLR4	toll-like receptor 4
T_{max}	time to C_{max}
ULN	upper limit of normal
WBC	white blood cell
YKL40	chitinase-like protein 1, a secreted glycoprotein associated with inflammation and tissue remodeling

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. Second, altered FLNA also links to toll-like receptor 4 (TLR4) to allow Aβ_{42} to persistently activate this receptor. 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 and plaques 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. 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 were all 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 in rats and dogs. A 6-month repeat dose oral toxicity study in rat (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 observable 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 animals, including increased 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. The NOAEL from this 6-month study was 50 mg/kg/day (equivalent to 300 mg/m^2). A second ongoing 6-month repeat dose oral toxicity study in rat will more accurately determine the 6-month NOAEL in rat. Doses are vehicle and 125 and 250 mg/kg/day.

In a 9-month toxicity study in dog (PTI-125-NC-050), the no observable effect level (NOEL) of simufilam was 25 mg/kg. The 200 mg/kg (high) dose was decreased to 150 at 1 month due to bodyweight loss thought unsustainable for 9 months. Clinical signs were salivation and a few instances of muscle fasciculations. There were no pathology findings, but the high dose was considered adverse due to two unexplained deaths. The 75 mg/kg/day NOAEL provides 38- and 19-fold safety margins by C_{max} and AUC over the 100 mg b.i.d. dose in patients.

2.3. CLINICAL STUDIES

2.3.1. A first-in-human Single Ascending Dose clinical trial

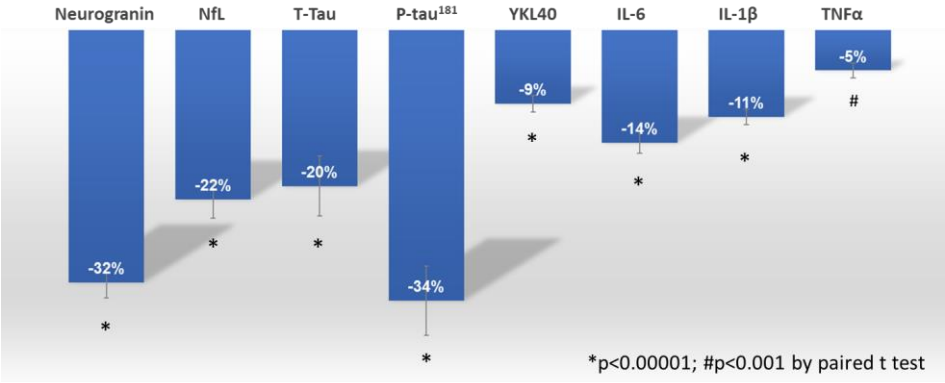
A first-in-human, double-blind, Single Ascending Dose clinical trial was conducted in healthy normal volunteers, age 18-45 with oral dosing solution. Doses were placebo, 50, 100 and 200 mg (equivalent to 31, 62, and 123 mg/m^2, respectively) administered to three different groups of volunteers. The study showed dose proportional PK, and there were no drug-related adverse events (AEs).

2.3.2. First-in-patient multidose clinical trial in mild-to-moderate AD patients

In a Phase 2a 28-day study, 13 mild-to-moderate AD patients received simufilam 100 mg b.i.d. as oral tablets. Patients were MMSE $\geq$ 16 and $\leq$ 24, age 50-85, with a CSF total tau/Aβ_{42} ratio $\geq$ 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] Aβ_{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 patients.

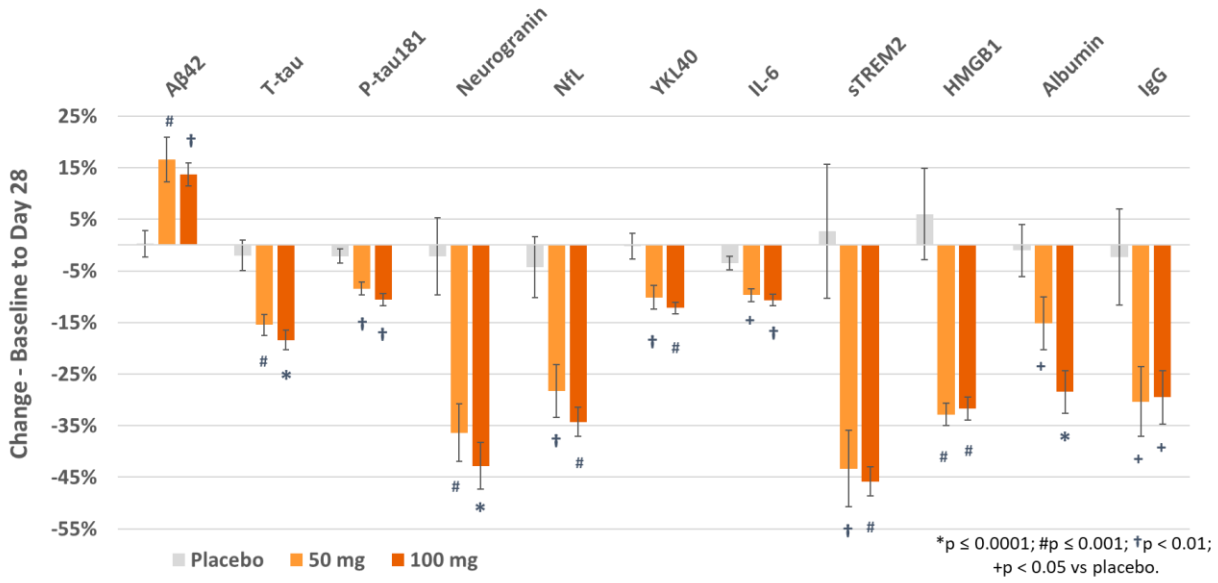
Fig. 1 Phase 2a Mean Change from Baseline to Day 28 in CSF biomarkers (±SEM)



2.3.3. Double-blind placebo-controlled clinical trial in mild-to-moderate AD patients

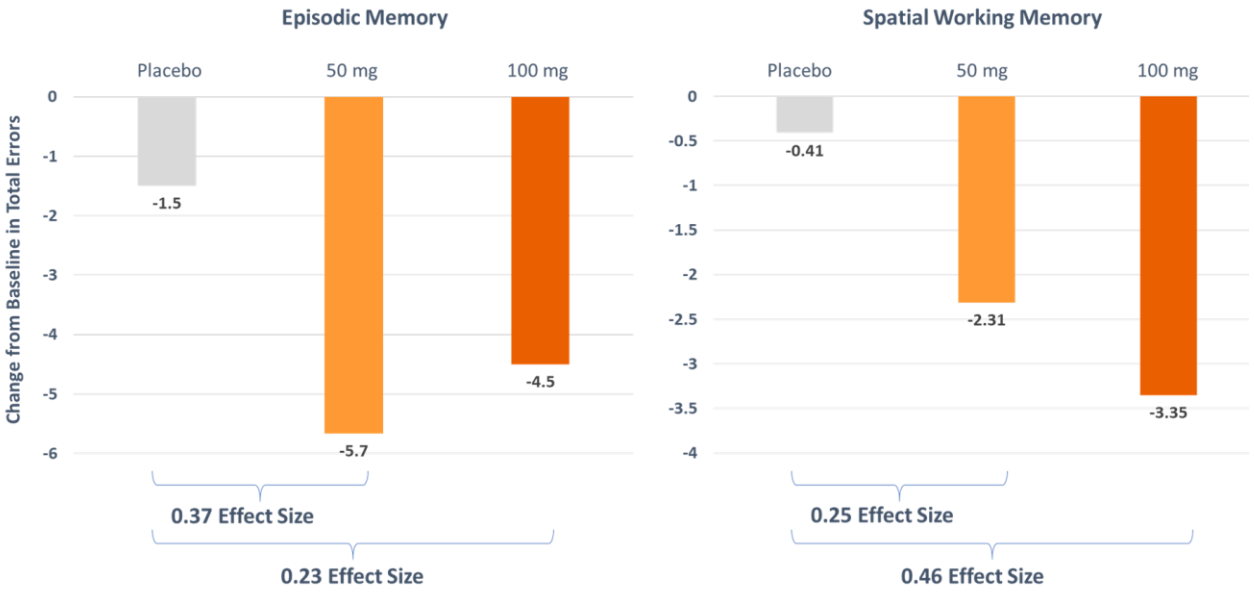
A Phase 2b randomized, placebo-controlled clinical trial of simufilam 50 or 100 mg tablets or placebo (1:1:1) enrolled 64 mild-to-moderate AD patients with MMSE 16-26. Both 50 and 100 mg doses significantly improved eleven CSF biomarkers of AD pathology, neurodegeneration, neuroinflammation and blood-brain 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 patient 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 our Phase 2a results in a well-controlled study.

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



The secondary endpoints in the Phase 2b trial were two cognitive measures using the Cambridge Neuropsychological Test Automated Battery. Patients were assessed on the Paired Associate Learning (PAL) test, measuring episodic memory, and a test of spatial working memory. The primary outcome measures for each were 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 37% and 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 17% and 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 trials, simufilam was well tolerated and no patients discontinued due to AEs.

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



2.3.4. Open-label safety clinical trial in mild-to-moderate AD patients

We are conducting a 1-year, open-label safety study in mild-to-moderate AD patients. The study was meant to offer open-label drug to participants of our two Phase 2 studies and is also enrolling new patients. In the first 50 patients to reach 6 months, simufilam improved cognition and behavior at 1, 3 and 6 months. ADAS-Cog11 scores improved 1.6 points and NPI scores improved 1.3 points from baseline at 6 months. Mean baseline MMSE was 22.1, and mean ADAS-Cog11 was 15.5 for these 50 patients.

3. STUDY OBJECTIVES

The objectives of this study are to establish 1-year safety and to investigate the effect of simufilam on biomarkers, cognition and neuropsychiatric symptoms during 12-month repeat-dose oral administration in mild-to-moderate AD patients, 50-85 years of age. An objective of the 6-month randomized withdrawal is to determine whether mild-to-moderate AD patients, age 50-85, who have completed a one-year open-label study of 100 mg b.i.d. simufilam and who continue with active dosing will show slower decline on ADAS-Cog11 and the NPI than patients who withdraw from this treatment.

4. SUMMARY OF STUDY DESIGN

The first 12 months is an open-label treatment of simufilam 100 mg b.i.d. for patients who completed prior Phase 2 studies PTI-125-02 and PTI-125-03. New patients are included so that up to 200 patients are enrolled in this study. Month 12 to Month 18 is a randomized withdrawal phase; patients will be randomized to continue taking simufilam 100 mg b.i.d. or matching placebo. Month 18 to Month 24 will be an additional 6 months of open-label simufilam 100 mg b.i.d. Simufilam and placebo will be administered as coated oral tablets. Patients who were enrolled prior to this amendment can continue upon reconsenting to the randomized withdrawal and final 6-month open-label portion.

All patients will provide consent to enroll into this study. Unless patients have a prior positive amyloid PET scan, MRI showing hippocampal volume loss or other prior evidence of AD, patients will undergo a CSF draw (if all other screening criteria are met) to confirm a total tau/Aβ_{42} ratio $\geq$ 0.28.

Patients will report to the clinic in the morning of Day 1. Prior to dosing, patients will complete the following baseline measures: ECG, vital signs, clinical labs, urinalysis, listen to heart and lungs, ADAS-Cog11, neuropsychiatric inventory (NPI), geriatric depression scale (GDS), and the C-SSRS. A blood sample will be collected for plasma-based biomarkers and genetic testing.

Patients will return to the clinic every month through Month 3 and every 1.5 months through Month 12. Visits on Months 4.5, 7.5 and 10.5 will include vital signs, listening to heart and lungs, AE monitoring, C-SSRS, and drug dispensation and accountability only and may be conducted by telemedicine, based on the judgement of the Investigator. After Month 12, visits will be on Months 13, 15, 18, 21 and 24. Patients completing Month 12 prior to availability of drug supply for the randomized withdrawal phase will continue with active treatment until drug supply is ready and therefore will have an additional "Withdrawal Day 1" visit before resuming with the Month 13 visit one month later.

PK blood samples will be obtained in the morning before dosing at return visits on Months 15 and 18.

Blood draws for clinical laboratory testing and urine collection for urinalysis will be performed at Day 1 and Months 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24. Safety assessments of vital signs and listening to heart and lungs will be conducted at all visits. ECGs will be conducted on Day 1 and Months 1, 3, 6, 9, 12, 18 and 24.

For plasma biomarkers, plasma samples will be collected on Day 1 prior to dosing and on Months 3, 6, 9, 12, 15, 18, 21 and 24. Plasma markers include SavaDx, the complementary diagnostic/biomarker, and a subset of CSF biomarkers (NfL, neurogranin, total tau, $A\beta_{42}$ and YKL40). For the first 50 patients who provided a screening CSF sample, an additional CSF sample will be collected at Month 6 or Month 12 (25 patients each Month 6 and Month 12). This sample will be used to assess CSF biomarker changes. These CSF draws will, however, become OPTIONAL after 50 patients have provided either a Month 6 or Month 12 CSF sample. Further, these optional Month 6 or Month 12 samples should NOT be obtained from patients who did not provide a CSF sample at screening.

An independent Data Safety Monitoring Board (DSMB), will meet periodically to review patient safety assessments and determine if dosing may continue.

5. SUBJECT SELECTION

5.1. STUDY POPULATION

Up to 200 patients will be enrolled in the study (male and female).

5.2. INCLUSION CRITERIA

All patients must comply with the following Inclusion Criteria:

1. Informed consent form (ICF) signed by the subject or legally acceptable representative. If a legally acceptable representative signs the ICF, a notation of capacity of the subject must be noted.
2. Patient has a caregiver or legal representative responsible for administering the drug and recording the time.
3. Ages ≥ 50 and ≤ 85 years

4. Clinical diagnosis of dementia due to possible or probable AD consistent with criteria established by a workgroup of the National Institute on Aging and the Alzheimer's Disease Association.
5. If female, postmenopausal for at least 1 year
6. Patient living at home, senior residential setting, or an institutional setting without the need for continuous (i.e. 24-h) nursing care
7. General health status acceptable for participation in the study
8. Fluency (oral and written) in English or Spanish
9. If receiving memantine, rivastigmine, galantamine or an AChEI, receiving a stable dose for at least 3 months (90 days) before screening. If receiving donepezil, receiving any dose lower than 23 mg once daily. Multiple medications are allowed.
10. The patient is a non-smoker for at least 3 years.
11. The patient or legal representative must agree to comply with the drawing of blood samples for the PK assessments, laboratory assessments and SavaDx.
12. MMSE-2 score ≥ 16 and ≤ 26 at screening, OR if > 26, must have evidence of AD pathology such as a prior CSF total tau/$A\beta_{42}$ ratio ≥ 0.28, an amyloid positive PET scan or hippocampal volume loss consistent with AD.

5.3. EXCLUSION CRITERIA

Patients meeting any of the following Exclusion Criteria will be excluded from the study:

1. Anything that in the opinion of the Investigator would preclude participation in a 2-year study.
2. BMI < 18.5
3. Positive urine drug screen.
4. Positive HIV, HCV or HbsAg screen.
5. Suicidality on C-SSRS
6. Exposure to an experimental drug other than simufilam, experimental biologic or experimental medical device within 3 months before screening
7. A medical condition that would interfere with a lumbar puncture
8. Residence in a skilled nursing facility and requiring 24 h care.
9. Clinically significant laboratory test results

10. Clinically significant untreated hypothyroidism (if treated, thyroid-stimulating hormone level and thyroid supplementation dose must be stable for at least 6 months before screening)
11. Insufficiently controlled diabetes mellitus, including requiring insulin or metformin >1000 mg/day.
12. Renal insufficiency (serum creatinine > ULN and clinically significant in the opinion of PI and/or Sponsor OR eGFR <60 ml/min/m^2 as estimated by either the MDRD or CKD-EPI equation)
13. Malignant tumor within 3 years before screening (except squamous and basal cell carcinoma or cervical carcinoma in situ or localized prostate cancer or localized stage 1 bladder cancer)
14. History of ischemic colitis or ischemic enterocolitis
15. Unstable medical condition that is clinically significant in the judgment of the investigator
16. Alanine transaminase (ALT) or aspartate transaminase (AST) > ULN or total bilirubin > ULN and clinically significant in the opinion of PI and/or Sponsor.
17. History of myocardial infarction or unstable angina within 6 months before screening
18. History of more than 1 myocardial infarction within 5 years before screening
19. Clinically significant cardiac arrhythmia (including atrial fibrillation), cardiomyopathy, or cardiac conduction defect (patients with a pacemaker are acceptable)
20. Symptomatic hypotension, or uncontrolled hypertension
21. Clinically significant abnormality on screening electrocardiogram (ECG), including but not necessarily limited to a confirmed QTc (Fridericia correction method) value ≥ 450 msec for males or ≥ 470 msec for females.
22. Stroke within 18 months before screening, or history of a stroke concomitant with onset of dementia
23. History of brain tumor or other clinically significant space-occupying lesion on CT or MRI
24. Head trauma with clinically significant loss of consciousness within 12 months before screening or concurrent with the onset of dementia
25. Onset of dementia secondary to cardiac arrest, surgery with general anesthesia, or resuscitation
26. Specific degenerative CNS disease diagnosis other than AD (e.g., Huntington's disease, Creutzfeld-Jacob disease, Down's syndrome, Frontotemporal Dementia, Parkinson's disease)

27. Wernicke's encephalopathy
28. Active acute or chronic CNS infection
29. Donepezil 23 mg or greater QD currently or within 3 months prior to enrollment
30. Discontinued AChEI < 30 days prior to enrollment
31. Antipsychotics; low doses are allowed only if given for sleep disturbances, agitation and/or aggression, and only if the subject has received a stable dose for at least 3 months before enrollment
32. Tricyclic antidepressants and monoamine oxidase inhibitors; all other antidepressants are allowed only if the subject has received a stable dose for at least 3 months before enrollment
33. Anxiolytics or sedative-hypnotics, including barbiturates (unless given in low doses for benign tremor); low doses of benzodiazepines and zolpidem are allowed only if given for insomnia/sleep disturbance, and only if the subject has received a stable dose for at least 3 months before enrollment
34. Immunosuppressants, including systemic corticosteroids, if taken in clinically immunosuppressive doses (Steroid use for allergy or other inflammation is permitted.)
35. Antiepileptic medications if taken for control of seizures
36. Chronic intake of opioid-containing analgesics
37. Sedating H1 antihistamines
38. Nicotine therapy (all dosage forms including a patch), varenicline (Chantix), or similar therapeutic agent within 30 days before screening
39. Clinically significant illness within 30 days of enrollment
40. History of significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, or metabolic disease
41. Loss of a significant volume of blood (> 450 mL) within 4 weeks prior to enrollment
42. COVID-19 infection within 3 months of screening

6. STUDY DRUG

6.1. STUDY DRUG PHYSICAL DESCRIPTION AND PREPARATION

Investigational simufilam and placebo will be supplied by Cassava Sciences as coated tablets in 70- or 200-count bottles. Several days of extra tablets are included in each bottle to allow flexibility of scheduling visits.

All remaining study drug will be returned to the sponsor or designee.

6.1.1. Storage

Bottles of study drug tablets should be stored at controlled room temperature, 20-25º C (68-77º F) and protected from light and moisture.

6.1.2. Drug Accountability

The Investigator will be responsible for monitoring the receipt, storage, dispensing and accounting of all study medications according to site SOPs. All invoices of study medication shipments 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

Patients will receive 100 mg simufilam b.i.d. during the open-label portions of the study and either 100 mg simufilam or matching placebo during the randomized withdrawal portion of the study. Simufilam or placebo tablets should be 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 3 months at entry.

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 patient or legal representative. The format and content of the ICF must be agreed upon by the Principal Investigator(s), the appropriate IRB and the Sponsor (or designee). The signed and dated ICF must be retained by the Investigator in the subject's file.

7.1. STOPPING CRITERIA

Liver chemistry threshold stopping criteria have been designed to assure patient safety and to evaluate liver event etiology during administration of Study Drug. Administration of Study Drug will be discontinued if any of the following liver chemistry stopping criteria occurs:

- ALT or AST ≥ 3 x ULN.
- ALT or AST ≥ 2.5 x ULN and total bilirubin ≥ 2 x ULN.
- ALT or AST ≥ 2 x ULN if associated with appearance or worsening of a rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia).
- ALT or GGT ≥ 2.5 x ULN that persists for ≥4 weeks.

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

An additional stopping criterion will be bodyweight loss of ≥ 2 kg resulting in a BMI < 18.5.

7.2. EVALUATIONS BY VISIT

7.2.1. Screening Visit 1 (Days -29 to 0)

Patients who completed PTI-125-02 < 60 days of study start will not be rescreened but will sign the ICF on Day 1 or earlier for this open-label extension.

For all other patients, the following will be completed in the screening visit:

- Informed Consent
- Review of Inclusion and Exclusion Criteria
- Medical history
- Review of concomitant medications
- Confirmation that the patient is either fully vaccinated for the COVID-19 virus at least 2 weeks prior to first dose of simufilam, or a positive serology test for the COVID-19 virus with no current symptoms
- If needed, CT scan to confirm I/E criteria, per investigator judgement
- MMSE-2 evaluation (prior patients do not need to meet 16 to 26 range)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Physical examination, including measurement of vital signs (blood pressure, temperature, pulse and respiratory rate), height, weight
- A 12-lead ECG (5-min supine)
- Laboratory assessments, including serum chemistry, hematology, urinalysis, and screens for HCV, HIV and HBsAg.
- Urine drug screen.

7.2.2. Screening Visit 2 (Days -28 to 0)

This CSF draw is **required for all NEW patients** meeting Screening Visit 1 criteria who do not have a prior positive amyloid PET scan or MRI showing hippocampal volume loss OR prior CSF biomarkers confirming AD. If Screening Visit 2 and Study Day 1 visit are combined, the CSF sample collection will occur 1-3 h after dosing and after the MMSE-2, ADAS-Cog11, NPI and GDS testing has been completed.

- CSF sample collection (5 mL)
- CSF samples should be held at the study site frozen at -70°C, pending shipping instructions from the Sponsor.

7.2.3. Study Day 1 (Dosing Initiation)

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

- Confirmation of Inclusion/Exclusion Criteria
- Review of concomitant medications
- Vital signs (blood pressure, temperature, pulse and respiratory rate), and weight
- Listen to heart and lungs
- ADAS-Cog11, NPI, GDS testing and C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the patient positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Blood sample collection for clinical laboratory tests
- Plasma sample collection for SavaDx and other plasma biomarkers.
- ECG

Patients will be administered 100 mg simufilam b.i.d. 1-2 h before or after a meal.

After dose on Study Day 1, the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate) at approximately 30 min, and 1 and 2 h post-dose.
- Adverse event monitoring

Clinic personnel will monitor the patients for AEs until discharge from the clinic. Upon investigator judgment, patients will be discharged with their supply of study

drug until the next visit. They will be instructed to take study drug twice daily, at least 1-2 h before or after a meal. A dose can be up to 4 h late, but if a dose is missed, the next dose should NOT be doubled.

All follow-up visits can be +/- five (5) days for flexibility. For all follow-up visits except Months 4.5, 7.5 and 10.5, patients will come to the clinic in the morning and will be instructed NOT to take their morning dose prior to coming to the clinic.

7.2.4. Follow-up Visits on Months 1, 3, 9, 13, 15, 21

Patients will return to clinic in the morning before taking their morning dose.

Within 30 min prior to dosing, the following assessments will be conducted:

- Blood sample collection for PK assessment (for Cmin – **Month 15 only**)
- Clinical laboratory tests (blood and urine) (All visits **except Month 13**)
- **Plasma** sample collection (from 8 mL whole blood) for SavaDx and other plasma biomarkers (All visits **except Months 1 and 13**)

After dose, the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate), and weight
- Listen to heart and lungs
- ECG (**Month 1 only**)
- Adverse event monitoring
- ADAS-Cog11, NPI, GDS and C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the patient positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Saliva collection for genetic testing (**Month 15 Visit only**)

7.2.5. Follow-up Visit on Month 2

Patients will return to clinic in the morning before taking their morning dose.

Within 30 min prior to dosing, the following assessments will be conducted:

- Clinical laboratory tests (blood and urine)

After dose, the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate), and weight

- Listen to heart and lungs
- Adverse event monitoring
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the patient positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.

7.2.6. Follow-up Visits on Months 4.5, 7.5 and 10.5

Patients will return to clinic at any time of day. The visit may be conducted by telemedicine, based on the judgement of the Investigator.

The following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate), and weight
- Listen to heart and lungs
- Adverse event monitoring
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the patient positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.

7.2.7. Follow-up Visits on Month 6 and 18

Patients will return to the clinic in the morning on the Month 6 Visit. Those patients undergoing a CSF draw will take their morning dose upon arrival (time of dosing to be recorded).

Patients will return to clinic in the morning before taking their morning dose.

Within 30 min prior to dosing, the following assessments will be conducted:

- Blood sample collection for PK assessment (for Cmin – **Month 18 only**)
- Clinical laboratory tests (blood and urine)
- Plasma sample collection (from 8 mL whole blood) for SavaDx and other plasma biomarkers.

After dose, the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse and respiratory rate), and weight
- Listen to heart and lungs

- Adverse event monitoring
- ECG
- ADAS-Cog11, NPI, GDS, and C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the patient positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- CSF sample collection at **Month 6** (time post-dose to be recorded) **only for the first 25 patients with a baseline CSF**. (The next 25 patients with a baseline CSF will have CSF drawn at Month 12). **Month 18** CSF draw is OPTIONAL for patients who provided a Month 6 or Month 12 CSF and is not an option for any other patients.

7.2.8. Month 12 and 24 Follow-up Visits

Patients will return to clinic in the morning before taking their morning dose. Patients who were enrolled prior to this amendment can terminate after completing the original 12-month open-label portion or can reconsent to the randomized withdrawal and final 6-month open-label portion. Month 12 morning dose in the clinic will be from Open-Label Period 1 bottle. Month 12 evening dose will be from the Randomized Period 2 bottle.

Within 30 min prior to dosing, the following assessments will be conducted:

- Clinical laboratory tests (blood and urine)
- Plasma sample collection (from 8 mL whole blood) for SavaDx and other plasma biomarkers.

After dose, the following assessments will be conducted:

- Full physical exam
- Adverse event monitoring
- MMSE-2
- ECG
- ADAS-Cog11, NPI, GDS, and C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the patient positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- CSF sample collection at Month 12 (time post-dose to be recorded) **for patients with a screening CSF who did not provide a CSF sample at Month 6. For those patients who provided a Month 6 CSF, this Month 12 CSF will be OPTIONAL. After 50 patients have provided either Month 6**

or Month 12 CSF, no additional patients will have CSF drawn after screening. No CSF will be drawn at Month 24.

For patients undergoing a CSF draw, CSF sample collection (5 mL) will occur 1-3 h after dosing and after the MMSE, ADAS-Cog11, NPI and GDS testing has been completed. These samples will be tested for CSF biomarkers.

Patients who complete Month 12 prior to availability of drug supply for the randomized withdrawal phase (Months 12 – 18) will be dispensed additional open-label simufilam and will return for a Withdrawal Day 1 Visit as appropriate.

7.2.9. Withdrawal Day 1 Visit – If Needed

This additional visit is **only for patients who complete Month 12 prior to availability of drug supply for the randomized withdrawal phase** (Months 12 – 18) and who have been dispensed additional open-label simufilam while waiting. Patients will return to the clinic at any time of day for the following assessments:

- ADAS-Cog11, NPI, GDS, and C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the patient positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.

These patients will return to the clinic one month later for the Month 13 visit and continue with the rest of the scheduled visits.

7.3. LABORATORY ASSESSMENTS

7.3.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed at screening, Day 1 pre-dose, and at Months 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24:

- 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, cholesterol, triglycerides, albumin, globulin, total protein, uric acid, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), lactose dehydrogenase (LDH).
- Urinalysis: color, specific gravity, pH, protein, sugar, ketones, occult blood, creatinine clearance calculation by Cockcroft-Gault equation (without requiring a 24-h urine collection).

7.3.2. Preparation of Whole Blood Samples for Lymphocyte and Plasma Biomarkers

Whole blood samples will be collected on **Day 1 and Months 3, 6, 9, 12, 15, 18, 21 and 24**. Blood samples (**8 mL total**) will be drawn into a Vacutainer® tube containing K_2EDTA. As advised by Sponsor, the blood may be spun down to separate the plasma (***all new patients***) OR shipped as whole blood (***patients with prior samples shipped as whole blood. These patients with prior samples shipped as whole blood will continue to have samples shipped as whole blood only through Month 12. Samples at Months 15, 18 21 and 24 will be spun to plasma***). Plasma should be frozen at -70°C and held until advised by the Sponsor to ship to: Dr. John Xu, Abilene Christian University, HAL Research Center Room 201, 1201 East Ambler Ave, Abilene, TX 79699. Whole blood should be shipped immediately at 4°C to: Dr. Hoau-Yan Wang, CUNY School of Medicine, SOM CDI 3370, 85 St. Nicolas Terrace, New York, NY 10027, or another lab. Do not ship samples on Friday.

7.3.3. Preparation of Plasma Samples for Pharmacokinetic Determination

At each blood collection for PK (pre-dose samples for C_{min} at Months 15 and 18 only, blood samples (4 mL) will be drawn into a Vacutainer® tube containing K_2EDTA. 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 between 4-5°C. Within 30 min of centrifuging, plasma (at least 1.5 mL) will be split into two aliquots, transferred to polypropylene tubes and stored at -20°C or below until analysis.

At the end of the study, PK samples will be shipped frozen on dry ice to: Worldwide Clinical Trials Bioanalytical Sciences, 8609 Cross Park Drive, Austin, TX 78754 for bioanalytical analysis of simufilam with a validated assay. The second set of samples will be shipped separately once receipt of the first set is confirmed.

7.3.4. Preparation of CSF samples

CSF will be collected and aliquoted into **5 ml Screw-Cap LoBind Eppendorf® tubes (#** 0030122356). CSF samples should be split into two aliquots of 2.5 mL. Samples will be held frozen at -70°C.

When notified by Sponsor, samples will be shipped to Dr. Wang at CUNY (address above) for biomarker analyses or another lab. Samples will be shipped frozen on dry ice (Mon – Wed).

7.3.5. Collection of Cheek Swab Saliva Samples for Genetic Testing

Saliva samples will be collected only at Month 15. Patients will refrain from eating or drinking 1 h prior to saliva collection. Each patient will be instructed to spit into a saliva collection tube. The saliva will be stored at -20°C until instructed to ship by the Sponsor.

8. EARLY DISCONTINUATION

Patients may choose to discontinue study drug or study participation at any time, for any reason, and without prejudice. Patients who discontinue may be replaced at Sponsor discretion.

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

- The reason for early study discontinuation.
- Vital signs (blood pressure, temperature, pulse and respiratory rate), weight, full physical examination, clinical laboratory tests, ECG, use of concomitant medications, and adverse events) should be obtained at discharge prior to release.
- Collection of plasma for biomarkers
- MMSE-2
- ADAS-Cog11, NPI and GDS (If the patient scores above 4 on the GDS assessment, a referral for further follow-up with the patient's primary care physician or psychiatrist is required. In addition, immediately administer the C-SSRS. If the C-SSRS indicates imminent risk for suicidality, defined as the patient positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, immediately contact the sponsor.)

9. ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

9.1. 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 electronic Case Report Form (eCRF) 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 eCRF 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 on the eCRF in appropriate medical terminology. The severity and the relationship to the study drug will be determined and reported on the CRF (see below).

9.2. 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 Adverse Event CRF.

9.3. 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 the study drug belongs to; or the AE abated on study drug discontinuation and reappeared upon re-challenge with the study drug.

These three categories are based on the Investigator's clinical judgment and 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 relationship of the AE to the study drug will be recorded in the eCRF.

9.4. 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 only listed elevated hepatic enzymes or hepatitis.

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

9.5. SERIOUS ADVERSE EVENTS REPORTING

The reporting of SAEs by the Sponsor to Regulatory Authorities (e.g., FDA) is a regulatory requirement.

All SAEs must be reported immediately **(within 24 h of learning of the event)** by telephone or notification via email through the EDC system to:

Nadav Friedmann, PhD, MD
Cassava Sciences, Inc.
Email: nfriedmann@cassavasciences.com
Phone: 925-788-4585

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.

A completed SAE report form must be sent within five (5) working days to the medical monitor. The Sponsor will report SAEs to the IRB and FDA as required.

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.

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 ICF. All patients experiencing an SAE will be seen by a Principal Investigator or designee as soon as feasible following the report of an SAE.

10. STATISTICAL CONSIDERATIONS

10.1. ANALYSIS POPULATIONS

All patients who receive study medication will be included in safety analyses. All patients who have sufficient data for biomarker, ADAS-Cog11, NPI and GDS analyses will be included in the analysis population for each measure individually.

10.2. PHARMACOKINETIC PARAMETERS

The only plasma PK parameters to be collected from this study are the C_{min} values from blood samples taken prior to dosing at Months 15 and 18.

10.3. STATISTICAL ANALYSIS

Biomarker endpoints to be analyzed include: 1) CSF $A\beta_{42}$, 2) CSF total tau 3) CSF p-tau181, 4) CSF neurofilament light chain, 5) CSF neurogranin, 6) CSF sTREM2, 7) plasma neurofilament light chain, 8) plasma neurogranin, 9) plasma total tau, 10) plasma $A\beta_{42}$, 11) SavaDx lymphocyte assay, 12) SavaDx plasma assay and 13) mTOR assay. These data will be analyzed by paired t test comparing baseline to Month 6 or Month 12. Other appropriate statistics may be performed to compare mild versus moderate patients.

The ADAS-Cog11, NPI and GDS endpoints will be analyzed by linear regression with pre-planned comparisons of mild versus moderate patients. Other appropriate statistics may be performed.

Month 12 to Month 18 ADAS-Cog11, NPI and GDS data will be analyzed by mixed model repeated measures (MMRM) analysis. Month 6/12 to Month 18 CSF biomarker data will be analyzed by ANCOVA for the effect of treatment with Month 6/12 value as the covariate, or by ANOVA.

10.4. 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.

10.5. SAMPLE SIZE

Up to 200 patients may be enrolled in this study. Eligible patients include those who completed PTI-125-03 and PTI-125-02 as well as new patients.

11. STUDY TERMINATION

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

12. DATA COLLECTION, RETENTION AND MONITORING

12.1. CASE REPORT FORMS

Electronic case report forms (eCRFs) will be used for each subject. The patients 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 patient number.

All clinical information requested in this protocol will be recorded in the eCRFs provided by CSI. In case of error, the correction will be noted, initialed and dated.

eCRFs must be reviewed and verified for accuracy by the Principal Investigator and signed-off before collection by the Sponsor (or CRO designee). Paper source documents, if used, will remain at the Investigator's site after study completion.

12.2. 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 eCRFs, 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 eCRF.

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

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

12.3. SUBJECT CONFIDENTIALITY

All reports and subject samples will be identified only by the assigned patient number and initials to maintain subject confidentiality. Additional subject confidentiality issues (if applicable) are covered in the Clinical Trial Agreement.

12.4. 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 use of the study drug, the Sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which 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.

12.5. 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.

12.5.1. Institutional Review Board

The protocol and Informed Consent Form 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 IRB approval must be provided to the Sponsor. Investigators are responsible for the following:

- Obtaining IRB approval of the protocol, Informed Consent Form, and any advertisements to recruit patients and IRB approval of any protocol amendments and Informed Consent Form revisions before implementing the changes.
- Providing the IRB with any required information before or during the study.
- Submitting progress reports to the IRB, as required, requesting additional review and approval, as needed; and providing copies of all relevant IRB communications to the Sponsor.
- Notifying the IRB within 15 calendar days of all SAEs and unexpected AEs related to study medications reported by the Sponsor to the Investigator.

12.6. INFORMED CONSENT FORM

The Sponsor (or designee) must review the Investigator's proposed ICF prior to IRB submission for approval. An IRB-approved copy of the Informed Consent Form is forwarded to the Sponsor.

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.

13. INVESTIGATOR RESPONSIBILITIES

The Investigator agrees to:

- Conduct the study in accordance with the protocol, except to protect the safety, rights, or welfare of patients.
- Personally conduct or supervise the study.
- Ensure that requirements for obtaining informed consent 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 Sponsor all changes in research activity and unanticipated problems involving risks to patients 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.

14. REFERENCES

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5. Hansson O, Seibyl J, Stomrud E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PETand predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimer's Dement 2018;14:1470-81.

15. APPENDIX A
Events Schedule

PROCEDURE	Screen Visit 1	Screen Visit 2	DAY 1	Month 1	Months 2, 4.5, 7.5 & 10.5	Months 3, 9, 15 & 21	Month 13	Months 6 & 18	Month 12 & 24	(With-drawal Day 1)
Informed Consent [a]	X								(X)	
Medical histories	X									
ECG	X		X	X				X	X	
CT scan	(X)									
Vital signs [d]	X		X	X	(X)	X	X	X	X	
Physical examination	X		*	*	(*)	*	*	*	X	
Biochemistry, hematology, urinalysis	X		X	X	Month 2 only	X		X	X	
MMSE-2	X								X	
Saliva collected for genetic testing						Month 15 only				
HCV, HBsAg & HIV screen	X									
Urine drug screen	X									
Drug dispensation			X	X	X	X		X	X[e]	X
Pre-dose blood sample for PK						Month 15 only		Month 18 only		
Adverse events			X	X	X	X	X	X	X	
Blood draw for biomarkers			X			X		X	X	
CSF draw		(X) [b]						(X) [c]	(X) [c]	
ADAS-Cog, NPI and GDS			X	X		X	X	X	X	X
C-SSRS	X		X	X	X	X	X	X	X	X

( ) indicates performed per investigator judgement or not for all patients
* Listen to heart and lungs
[a] Patients who did not initially consent for a 2-year study should be reconsented at their next study visit.
[b] Patients who have a prior amyloid PET or other confirmation of AD can bypass this baseline CSF draw

[c] Only for patients with a baseline CSF. Patients with a baseline CSF have the option to do a Month 6 or 12 CSF draw. Month 18 CSF draw is an option only for patients who provided Month 6 or 12 CSF.
[d] Include weight for BMI calculation
[e] Drug dispensation only at Month 12
NB: Withdrawal Day 1 is only for patients who complete Month 12 prior to drug supply availability for the randomized withdrawal.