CLINICAL RESEARCH PROTOCOL

PROTOCOL PTl-125-05

A Four-way Crossover Food Effect and Bioequivalence Pharmacokinetic Study of Simufilam in Healthy Volunteers

Sponsor: **Cassava Sciences, Inc.**

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Protocol Date: March 5, 2021

Confidentiality

Cassava Sciences, Inc.

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Cassava Sciences, Inc.

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Signature of Agreement for Protocol PTI-125-05

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-cog	Alzheimer's Disease Assessment Scale – cognitive subscale
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
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
CRO	contract research organization
CSF	cerebrospinal fluid
CSI	Cassava Sciences, Inc.
CT	computed tomography
ECG	electrocardiogram
CRF	case report form
EDTA	ethylenediaminetetraacetic acid
FDA	Federal Drug Association
FIH	first in human
FLNA	filamin A
GCP	good clinical practice
GLP	good laboratory practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HED	human equivalent dose
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	independent review board
LOQ	limit of quantitation
MMSE	Mini Mental State Evaluation
NMDAR	N-methyl D-aspartate receptor
NOAEL	no observable adverse effect level

NOEL	no observable effect level
PK	pharmacokinetics
SavaDx	blood-based diagnostic/biomarker candidate
RBC	red blood cell
SAE	serious adverse event
Simufilam	small molecule drug candidate to treat AD
SOP	standard operating procedure
Tmax	time to Cmax
ULN	upper limit of normal
WBC	white blood cell

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 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 6-month repeat dose oral toxicity study in rat, pending pathology, will more accurately determine the 6-month NOAEL in rat. Doses are vehicle and 125 and 250 mg/kg/day.

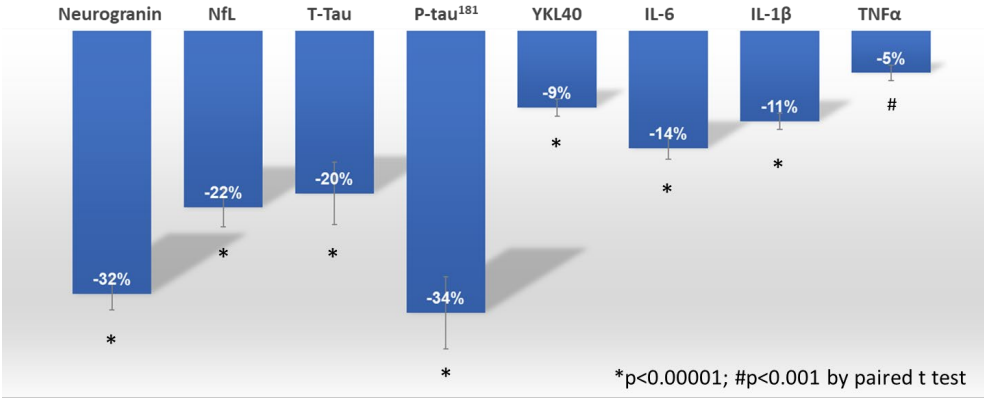
In a 9-month toxicity study in dog (PTI-125-NC-050), the no observable effect level (NOEL) of simufilam was 25 mg/kg. The 200 mg/kg (high) dose was decreased to 150 at 1 month due to bodyweight loss thought unsustainable for 9 months. Clinical signs were salivation and a few instances of muscle fasciculations. 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, respectively, over the 100 mg b.i.d. dose in patients.

2.3. CLINICAL STUDIES

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).

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.

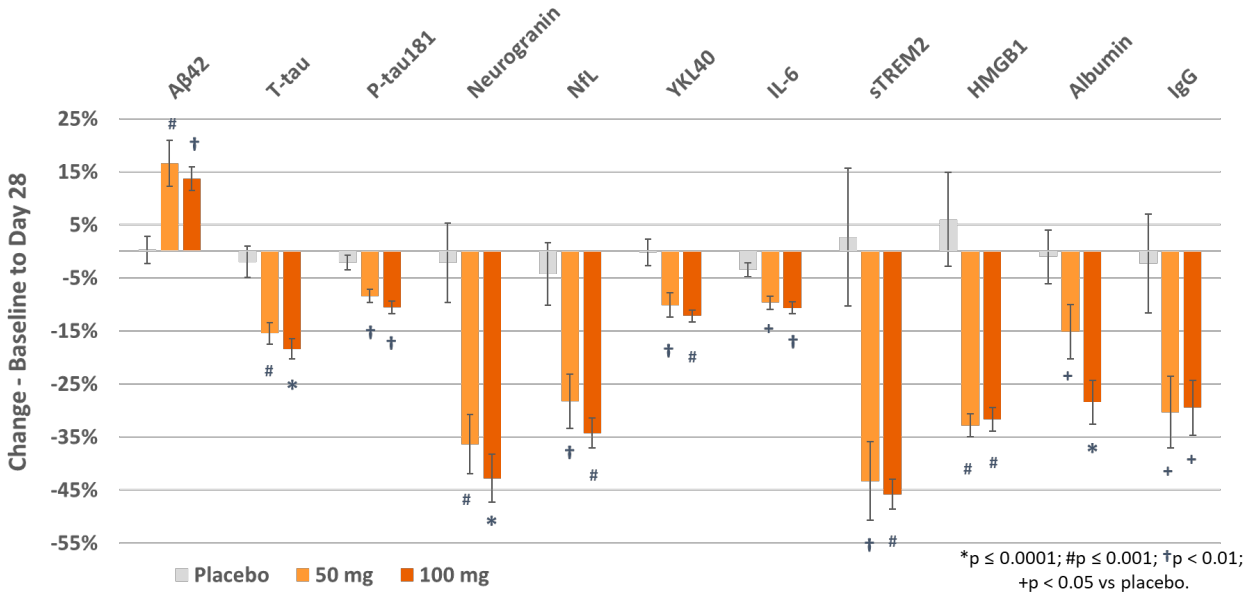
Fig. 1 Mean Change from Baseline to Day 28 in CSF biomarkers (±SEM)



Pharmacokinetic analysis indicated minimal accumulation (ratio 1.36, based on overall exposure) and consistent clearance and apparent volume of distribution across study days. Steady state concentration was achieved by Day 7 and were maintained through Day 28.

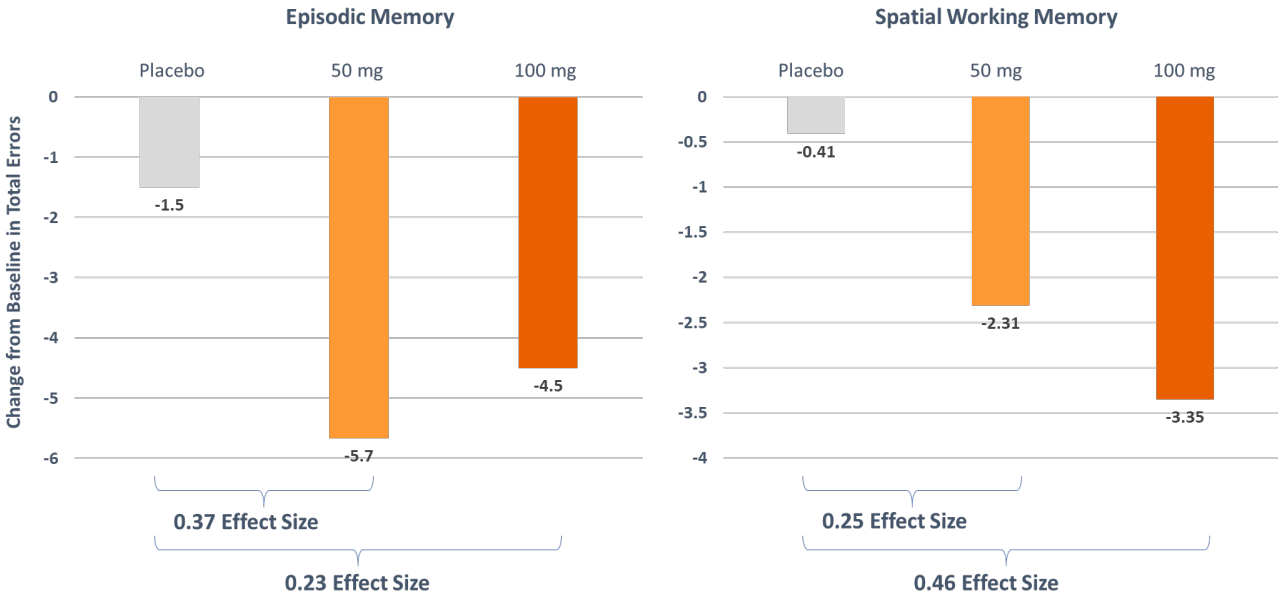
A Phase 2b randomized clinical trial of simufilam 50 or 100 mg tablets or placebo (1:1:1) enrolled 64 mild-to-moderate AD patients. Both doses significantly improved eleven CSF biomarkers of AD pathology, neurodegeneration, neuroinflammation and blood-brain barrier integrity (**Fig. 2**). CSF biomarker analyses were conducted blind to treatment and timepoint by an outside lab. These data suggest disease modification and replicate the 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



To benefit participants of previous one-month studies and to assess longer-term clinical safety of simufilam, a 1-year, open-label clinical trial of approximately 100 mild-to-moderate AD patients is ongoing. All prior patients were eligible, and new patients (MMSE 16-26) can enroll. All new patients have a baseline CSF draw, and change in biomarkers will be evaluated after 6 or 12 months. Additionally, cognition is being assessed with the ADAS-Cog and neuropsychiatric symptoms by the NPI.

3. STUDY OBJECTIVES

The objectives of this study are 1) to assess the effect of food on the rate and extent of absorption of simufilam, and 2) to compare the pharmacokinetic profile of the Phase 3 formulation of simufilam to that of the earlier Phase 2 formulation. The new Phase 3 formulation has a higher percentage of active ingredient and is therefore smaller with a slightly different shape.

4. SUMMARY OF STUDY DESIGN

This is a single-center, randomized, four-treatment, four-sequence crossover study in healthy volunteers to estimate the effect of food on the PK of simufilam following oral dosing of the Phase 3 simufilam 100 mg tablet. Additionally, the relative bioavailability of the Phase 3 tablet will be compared to the earlier Phase 2 simufilam 100 mg tablet, both in the fasted state. A total of twenty four (24) healthy volunteers (12 male and 12 female) will be enrolled into this study. Subjects will be randomly assigned to one of four treatment sequences (6 subjects/sequence) as shown in **Table 6**.

Table 6 Treatment Sequence

Sequence	Treatment Period 1				Treatment Period 2				Treatment Period 3				Treatment Period 4			
	Fasted	High	Low	Phase 2 Tablet	Fasted	High	Low	Phase 2 Tablet	Fasted	High	Low	Phase 2 Tablet	Fasted	High	Low	Phase 2 Tablet
Sequence A (n = 6)				X			X		X					X		
Sequence B (n = 6)	X							X		X					X	
Sequence C (n = 6)		X			X						X					X
Sequence D (n = 6)			X			X						X	X			

During each 48-h treatment period, subjects will be given a single oral dose of simufilam as displayed in **Table 6**. The administration of each dose of study drug will be separated by a 48-hour washout period. PK blood samples will be obtained prior to dosing and at specified intervals during the study (0-48 h post-dose for Treatment Periods 1 - 4). The observation period for safety will continue through the incarceration period.

5. SUBJECT SELECTION

5.1. STUDY POPULATION

A total of 24 subjects will be enrolled in the study (12 males and 12 females).

5.2. INCLUSION CRITERIA

Each patient must comply with the following Inclusion Criteria:

1. Male or female subjects Ages ≥ 18 and ≤ 45 years
2. BMI of 18 – 30 Kg/m²
3. Informed consent form (ICF) signed by the subject
4. General health status acceptable for participation in the study as determined by medical history, review of current medication, physical examination, and laboratory results
5. Females must be of non-childbearing potential (defined as surgically sterile [i.e. had a bilateral tubal ligation, hysterectomy, or bilateral oophorectomy at least 6 months before the first dose of study medication] or postmenopausal with amenorrhea for at least 1 year before the first dose of study medication [serum FSH levels consistent with postmenopausal status i.e., greater than 40 mIU/mL]) or agree to use an acceptable form of birth control (see Section 5.4) from screening until 14 days after study completion.Fluency (oral and written) in English
6. The patient must agree to comply with the drawing of blood samples for the PK assessments, laboratory assessments and plasma biomarkers
7. The subject is willing and able to remain at the study site for the duration of the study

5.3. EXCLUSION CRITERIA

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

1. The subject has any relevant deviations from normal in physical examination, electrocardiogram (ECG), or clinical laboratory tests, as evaluated by the investigator.
2. The subject has had a clinically significant illness within 30 days of this study.
3. The subject has a history of significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, or metabolic disease.

4. Subject is taking prescription CNS medication.

5. The subject has used alcohol, grapefruit, grapefruit juice, caffeine or xanthine-containing products 48 h before dosing or intends to use any of these products during the study.

6. The subject has a history of substance abuse or a current positive ethanol urine test or positive urine drug screen.

7. The subject has a positive serum hepatitis B surface antigen or positive HCV antibody test.

8. The subject has a positive HIV test.

9. The subject has a current positive urine cotinine test.

10. The subject has participated in another drug study in the past 30 days.

11. The subject has donated or lost a significant volume of blood (>450 mL) within 4 weeks of the study.

12. The subject is unwilling to reside in the study unit for the duration of the study or to cooperate fully with the investigator or site personnel.

13. Covid-19 infection within the past 3 months

5.4. BIRTH CONTROL

Subjects will be advised to use one of the following forms of birth control during the study:

- Postmenopausal (at least 2 years before dosing)
- Vasectomized partner (at least 6 months before dosing)
- Surgical sterilization (bilateral tubal ligation – tubes tied, hysterectomy – removal of the uterus, bilateral oophorectomy – removal of both ovaries) at least 6 months before dosing
- Non-surgical permanent sterilization (e.g., Essure® procedure) at least 3 months before dosing
- Double barrier (diaphragm with spermicide; condoms with spermicide)
- Intrauterine device (IUD)
- Abstinence (you must agree to use a double barrier method if you become sexually active during the study)
- Implanted or intrauterine hormonal contraceptives in use for at least 6 consecutive months before study dosing and throughout the study duration
- Oral, patch, or injected contraceptives, or vaginal hormonal device (i.e. NuvaRing®), in use for at least 3 consecutive months before study dosing and throughout the study duration

6. STUDY DRUG

6.1. SIMUFILAM PHYSICAL DESCRIPTION AND PREPARATION

Investigational simufilam will be supplied by Cassava Sciences as coated tablets.

6.1.1. Storage

Bottles of simufilam 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

All subjects will receive simufilam as follows:

Treatment Period 1 Day 1*	Washout Day 2	Treatment Period 2 Day 3*	Washout Day 4	Treatment Period 3 Day 5*	Washout Day 6	Treatment Period 3 Day 7*	Day 8
1 tablet simufilam	No dose	1 tablet simufilam	No dose	1 tablet simufilam	No dose	1 tablet simufilam	No dose

* Subjects will take the current tablet formulation in a fed or fasted state or the previous Phase 2 tablet in a fasted state, depending on the sequence group.

When receiving simufilam in a fasted state, subjects will fast for at least 10 h prior to dosing. Water will be allowed until 1 h before dosing. The simufilam tablet will be administered with 240 mL of water, and no additional water will be allowed until 1 h post-dose. No food will be allowed until 4 h post-dose.

Subjects to be administered simufilam in a fed state will consume either a high-fat or low-fat breakfast. The high-fat breakfast will consist of two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 oz hash brown potatoes, and 8 oz whole milk. The low-fat breakfast will consist of one slice of toast with jelly, 1 ¼ oz raisin bran cereal, one banana, 4 oz skim milk, and 6 oz orange juice. Subjects will be instructed to

eat the meal within 30 min. The simufilam tablet will be administered 30 min after the start of the meal with 240 mL water, and no additional water will be allowed until 1 h post-dose. No additional food will be allowed until 4 h post-dose.

6.3. CONCOMITANT MEDICATIONS

Use of non-prescription medication will be prohibited for 48 h before initial drug administration and during the study. Use of alcohol, grapefruit, grapefruit juice, and caffeine- or xanthine-containing products is also prohibited 48 h before dosing and during the study.

6.4. STUDY PROCEDURES

Appendix A presents the Schedule of Activities.

Prior to any study-related activities, the ICF must be signed and dated by the subject. 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.

6.5. EVALUATIONS BY VISIT

6.5.1. Screening Period

The following will be completed within 28 days prior to administration of the study medication:

- Informed Consent (written consent must be obtained prior to conducting any screening activities)
- Review of Inclusion and Exclusion Criteria
- Medical history including review of current medication
- Physical examination, including measurement of vital signs (after a 3-minute sitting period), height, weight and BMI
- A 12-lead ECG

The following laboratory assessments will be completed at screening.

- Serum chemistry, hematology, and urinalysis
- Urine drug screen: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, and cannabinoids

- Ethanol urine test
- Urine cotinine
- HIV test
- HBsAg, HCV Antibody tests

6.5.2. Check-in (Day 0)

Subjects will check into the clinic on the day prior to dosing, and will remain confined to the clinic for the duration of the study. Upon check-in, the following assessments will be conducted:

- Ethanol urine test
- Urine drug screen/urine cotinine
- Pregnancy test for females
- COVID-19 testing (nasopharyngeal swab test)
- Review of concomitant medication
- Confirmation of inclusion/exclusion criteria

6.5.3. Treatment Period 1 – Day 1

Note: Study Day 1 is defined as the calendar day the study drug is first administered.

According to each subject's sequence assignment, subjects to receive the first dose **fasted** will fast for at least 10 h prior to dosing. Water will be allowed until 1 h before dosing.

On the morning of Study Day l, prior to dosing, subjects to be administered simufilam in a **fed** state will consume either a **high-fat** or **low-fat** breakfast, according to their sequence assignment and as described in the Section 6.2 above. The simufilam tablet will be administered 30 min after the start of the meal.

For all subjects, the following will be conducted in the morning of Study Day 1:

- Blood draw for clinical laboratory tests, chemistry hematology and urine sample for urinalysis.
- Vital signs after a 3-minute sitting period (blood pressure, pulse, temperature and respiration rate) within 1 h before dosing
- Blood sample collection for baseline PK assessment (Time = 0) within

1 h before dosing

The simufilam tablet will be administered with 240 mL of water, **30 min after the start of the meal** (if dosing in a fed state). No additional water will be allowed until 1 h post-dose. No food will be allowed until 4 h post-dose.

After dosing, the following assessments will be conducted:

- Vital signs (blood pressure, pulse and respiration rate) at approximately 30 and 90 min, and 4, 8, 12, h post-dose (within 15 min of nominal time)
- Blood samples will be drawn at 20, 40, and 60 min and at 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 h after dosing for PK assessments (as close as possible to nominal time, but within 5 min for timepoints up to 3 h and within 15 min thereafter).
- Adverse event monitoring

All subjects will receive a meal 4 h post-dose. All meals for the first 24 h after dosing will be served at a fixed time interval after dose administration, such that meals are served in a staggered fashion.

6.5.4. Washout Periods – Days 2, 4 and 6

The following assessments will be conducted:

- Blood sample collection for PK prior to breakfast
- Vital signs (blood pressure, temperature, pulse and respiratory rate) at approximately 4 and 12 h after the PK sample collection
- Adverse event monitoring

6.5.5. Treatment Periods 2, 3 and 4 – Days 3, 5 and 7

According to each subject's sequence assignment, subjects to receive the first dose **fasted** will fast for at least 10 h prior to dosing. Water will be allowed until 1 h before dosing.

On the morning of Study Days 3, 5, and 7, prior to dosing, subjects to be administered simufilam in a **fed** state will consume either a **high-fat** or **low-fat** breakfast, according to their sequence assignment and as described in the Section 6.2 above. The simufilam tablet will be administered 30 min after the start of the meal.

The following will be conducted in the morning of Study Days 3, 5, and 7:

- Vital signs, within 1 h before dosing (blood pressure, pulse, temperature and respiration rate)
- Blood sample collection for PK assessment, within 1 h before dosing (Time = 0)

The simufilam tablet will be administered with 240 mL of water, **30 min after the start of the meal** (if dosing in a fed state). No additional water will be allowed until 1 h post-dose. No food will be allowed until 4 h post-dose.

After dosing, the following assessments will be conducted:

- Vital signs (blood pressure, pulse and respiration rate) at approximately 30 and 90 min, and 4, 8, 12, h post-dose (within 15 min of nominal time)
- Blood samples will be drawn at 20, 40, and 60 min and at 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 h after dosing for PK assessments (as close as possible to nominal time, but within 5 min for timepoints up to 3 h and within 15 min thereafter).
- Adverse event monitoring

All subjects will receive a meal 4 h post-dose. All meals for the first 24 h after dosing will be served at a fixed time interval after dose administration, such that meals are served in a staggered fashion.

6.5.6. Day 8

The following tests will be performed at Day 8 before discharge:

- Blood sample collection for PK prior to breakfast
- Blood draw for clinical laboratory tests, chemistry hematology and urine sample for urinalysis
- Vital signs (blood pressure, temperature, pulse and respiratory rate)
- Physical examination, excluding height, weight and BMI
- A 12-lead ECG
- Adverse event monitoring

6.6. LABORATORY ASSESSMENTS

6.6.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed at **Screening, at Day 1** time 0 (pre-dose) and at **Day 8 prior to discharge**:

- Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count
- Serum Chemistry: glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, uric acid, phosphorus, calcium, total protein, albumin, globulin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, lactose dehydrogenase (LDH)
- Urinalysis: color, specific gravity, pH, protein, sugar, ketones, occult blood

6.6.2. Preparation of Plasma Samples for Pharmacokinetic Determination

At each blood collection for PK, blood samples (4 mL) will be drawn into a Vacutainer® tube containing K2EDTA and 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 (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 or when advised by Sponsor, 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 when requested by the sponsor.

7. 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 the discretion of the Sponsor.

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), full physical examination, clinical laboratory tests, ECG, use of concomitant medications, and adverse events) should be obtained at discharge prior to release.

8. ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

8.1. 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 on the AE CRF in appropriate medical terminology. The severity and the relationship to the study drug will be determined and reported on the CRF (see below).

8.2. 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.

8.3. 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 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 Adverse Event CRF.

8.4. 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.

8.5. 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 their EC/IRB.

All SAEs must be reported immediately **(within 24 h of learning of the event)** by telephone 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 faxed within five working days to the medical monitor. SAEs must also be reported to the responsible EC/IRB immediately.

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

9. STATISTICAL CONSIDERATIONS

9.1. RANDOMIZATION

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

9.2. ANALYSIS POPULATIONS

All subjects who receive one dose of study medication will be included in the safety analyses. Any subject who did not complete all 4 study periods will be excluded from the PK analysis. The PK samples from subjects who drop out early will be analyzed and reported in the data listings.

9.3. PHARMACOKINETIC ANALYSIS

Pharmacokinetic Methods

Plasma concentration-time data will be analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.1, Certara, L.P.) in conjunction with the internet-accessible implementation of Pharsight® Knowledgebase Server™ (PKSO; Version 4.0.4, Certara, L.P.). Concentration-time data that are below the limit of quantification (BLQ) will be treated as zero in the data summarization and descriptive statistics.

In the pharmacokinetic (PK) analysis, BLQ concentrations will be treated as zero from time-zero up to the time at which the first quantifiable concentration will be observed; embedded and/or terminal BLQ concentrations will be treated as "missing." Actual sample times relative to the time of dose will be used in the PK analysis.

The following PK parameters will be calculated (but may not be limited to):

C_{max}	The maximum concentration determined directly from individual concentration-time data

T_{max}	Time to reach maximum concentration
AUC_{last}	Area under the curve to the time of the last quantifiable concentration, calculated using the linear trapezoidal method
AUC_{inf}	Area under the curve extrapolated to infinity; calculated as: $AUC_{inf} = AUC_{last} + C_{last}/\lambda_z$
C_{last}	The last quantifiable concentration determined directly from individual concentration-time data
T_{last}	Time of the last quantifiable concentration
λ_z	The observed elimination rate constant; estimated by linear regression through at least three data points in the terminal phase of the log concentration-time profile
$T_{1/2}$	The observed terminal elimination half-life calculated as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$

Note: λ_z and parameters calculating using λ_z (AUC_{inf} and $T_{1/2}$) will be reported only if an apparent elimination phase is observed.

Statistical Procedures

Natural log transformed AUC_{inf} (if data permit), AUC_{last}, and C_{max}, will be analyzed using a mixed effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

For the food effect assessment, simufilam in the fasted state will be the intended reference treatment. The following comparisons will be made:

High-fat vs. Fasted

Low-fat vs. Fasted.

Phase 2 tablet formulation vs. current tablet formulation (both Fasted).

9.4. SAFETY ANALYSIS

Adverse events reported on case report forms will be mapped to preferred terms and organ systems using the MedDRA mapping system. For each preferred term event, frequency counts and percentages will be calculated by treatment period. Vital signs and clinical laboratory results will be descriptively summarized in terms of change from screening values.

9.5. SAMPLE SIZE

Twenty-four (24) subjects will be enrolled in this study. Sample size was determined by estimating the intrasubject variability for log-transformed data from previous studies of simufilam. A sample size of twenty four subjects is expected to provide 80% power to obtain 90% confidence intervals for the geometric mean ratios of C_{max} and the AUCs.

10. STUDY TERMINATION

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

11. DATA COLLECTION, RETENTION AND MONITORING

11.1. CASE REPORT FORMS

Case report forms (CRFs) will be provided for each subject. 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 Study Identification Number and initials.

All clinical information requested in this protocol will be recorded on the CRFs provided by the Sponsor using legible entries with a black ballpoint pen. If an error is made, a single line will be drawn through the error and the correct response will be written adjacent to the error, and initialed and dated.

CRFs must be reviewed and verified for accuracy by the Principal Investigator and signed-off before collection by the Sponsor (or CRO designee). A copy of the CRF will remain at the Investigator's site at the completion of the.

11.2. 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 CRFs, 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 to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived. Investigators are

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

The Investigator is responsible for maintaining adequate case histories in each subject's source records. The Sponsor reserves the right to terminate the study for the Investigator's refusal to supply source documentation of work performed in this clinical trial.

11.3. SUBJECT CONFIDENTIALITY

All reports and subject samples will be identified only by Study Identification Number and initials to maintain subject confidentiality. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

11.4. 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 study Sponsor. Financial compensation for lost wages, disability or discomfort due to the study is not available.

11.5. 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.

11.5.1. 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.

11.6. INFORMED CONSENT FORM

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

The Informed Consent Form 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 Informed Consent Form must be signed and dated before the subject enters the study. The original Informed Consent Form and any amended Informed Consent Form, signed and dated, must be retained in the subject's file at the study site and a copy must be given to the subject.

12. 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 IRB and 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.

13. REFERENCES

1. Burns LH, Wang H-Y. Altered filamin A enables amyloid beta-induced tau hyperphosphorylation and neuroinflammation in Alzheimer's disease. Neuroimmunol Neuroinflammation 2017;4:263-71.
2. Wang H-Y, Lee K-C, Pei Z, Khan A, Bakshi K, Burns L. PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis. Neurobiol Aging 2017;55:99-114.
3. Wang H-Y, Bakshi K, Frankfurt M, et al. Reducing amyloid-related Alzheimer's disease pathogenesis by a small molecule targeting filamin A. J Neurosci 2012;32:9773-84.
4. Wang H-Y, Pei Z, K.-C. Lee K-C, et al. PTI-125 reduces biomarkers of Alzheimer's disease in patients. J Prevent Alzheimer's Disease 2020;7:256-64.

14. APPENDIX A – SCHEDULE OF ACTIVITIES

PROCEDURE	SCREENING *(Days -28 to Day -1)*	DAY 0 CHECK-IN	DAY 1 *Time = 0*	DAY 2 4 & 6	DAY 3 5 & 7	DAY 8 DISCHARGE
Informed Consent	X					
COVID-19		X				
Medication and medical histories	X	X				
Ethanol urine test	X	X				
Urine drug screen/ Urine cotinine	X	X				
Pregnancy test		X				
Review of inclusion/ exclusion criteria	X	X				
Drug administration			X		X	
Physical examination	X					X
ECG	X					X
Biochemistry, hematology, urinalysis	X		X			X
HCV, HBsAG & HIV screen	X					
Adverse events			X	X	X	X
Vital signs	X		X	X	X	X
Blood sample collection for PK analysis			X	X	X	X