CLINICAL RESEARCH PROTOCOL

PROTOCOL PTl-125-10

AN OPEN-LABEL, LONG-TERM EXTENSION STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF SIMUFILAM 100 MG TABLETS IN PARTICIPANTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE

SPONSOR:

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Confidentiality

SUMMARY OF PROTOCOL AMENDMENT #3
(New text is underlined, omitted text is struck through)

~~**LIST OF FIGURES**~~

1. LIST OF ABBREVIATIONS

Updated:

~~3xTg~~	~~triple transgenic~~
~~ADME~~	~~absorption, distribution, metabolism, excretion~~
CDR	Clinical Dementia Rating
~~ELISA~~	~~enzyme-linked immunosorbent assay~~
EoT	End of Treatment
~~hERG~~	~~human ether-a-go-go related gene~~
~~IgG~~	~~Immunoglobulin~~
~~ISLT~~	~~International Shopping List Test~~
~~NMDAR~~	~~N-methyl D-aspartate receptor~~
~~NOEL~~	~~no observable effect level~~
~~PAL~~	~~Paired Associate Learning~~
~~SavaDx~~	~~blood-based diagnostic/biomarker candidate~~
~~TLR4~~	~~toll-like receptor 4~~
Wk	Week
~~YKL40~~	~~chitinase-like protein 1, a secreted glycoprotein associated with inflammation and tissue remodeling~~

2.1 Mechanism of Action

Updated: 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~~, through actions involving filamin A (FLNA), prevents~~ing two~~ beta amyloid$_{1-42}$ (Aβ_{42})-induced toxic signaling cascades. Aβ_{42}, in monomer or small oligomer form, hijacks the α7-nicotinic acetylcholine receptor (α7nAChR) and signals via this receptor to hyperphosphorylate tau. ~~This signaling requires the recruitment of altered FLNA to this receptor. In addition, altered FLNA also links to toll-like receptor 4 (TLR4) to allow Aβ_{42} to persistently activate this receptor, leading to inflammatory cytokine release and neuroinflammation. Normal FLNA does not associate with either α7nAChR or TLR4. In addition to disrupting the normal functions of α7nAChR and tau protein, Aβ_{42}'s toxic~~

~~signaling to hyperphosphorylate tau leads to the signature tangles in AD brain.~~ Simufilam disrupts the association between $A\beta_{42}$ and the α7nAChR[1]. In addition, $A\beta_{42}$ activates toll-like receptor 4 leading to inflammatory cytokine release and neuroinflammation. 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 compared to control mice[1]. 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/m²/day).~~

Changed: 2.2 Safety pharmacology and toxicology
Changed to: 2.2 Nonclinical testing program

2.2 Updated to:
A robust nonclinical, absorption, distribution, metabolism, and excretion ~~ADME~~, safety pharmacology, ~~and~~ general and genetic toxicology program has been conducted with simufilam. Additional nonclinical studies, including carcinogenicity studies, are ongoing. A process impurity occurring in the drug substance, CML 1497, has been fully qualified for safe clinical use; additional studies with human metabolites are currently underway. ~~*In vitro* metabolic profiling showed minimal metabolism across several species including humans. Simufilam was rapidly absorbed and eliminated in *in vivo* studies in rat and dog with nearly 100% oral bioavailability, a 2.67-h half-life in dog, dose-proportional PK and no accumulation. Simufilam does not inhibit or induce major CYP450 enzymes, nor is a substrate or inhibitor of major human drug transporters at clinically relevant concentrations.~~

In vitro assays and safety pharmacology studies in rat and dog showed no off-target pharmacological effects on cardiovascular systems or respiratory function, or any adverse neurobehavioral effects.

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 electrocardiogram (ECG) parameters in the dog cardiovascular study. The *in vitro* human ether-a-go-go-related gene ~~hERG~~ test for cardiotoxicity also indicated no adverse effect.

PK, biodistribution, metabolism, and excretion studies were conducted to assess the bioavailability, biodistribution, mass balance, and excretion of simufilam and to determine its metabolic fate in vitro and in vivo. Oral bioavailability was high in rat and dog. Toxicokinetic studies were included in the toxicology studies to ascertain levels of systemic exposure. Rat biodistribution studies showed near 100% total mean recovery of oral dose radioactivity; urinary excretion accounted for close to 60% of the dose, with the remainder found in bile and feces. Quantitative Whole-Body Autoradiography indicated that simufilam was widely distributed to tissues. The metabolite radioprofiling and identification phase of the mass balance and PK study in rats indicated that simufilam was extensively metabolized in the rat and metabolites were excreted in urine, bile and feces. Elimination was rapid but incomplete at 24 hours.

An exploratory metabolite searching, identification, and relative abundance determination was conducted on plasma samples from a 5-Day multiple dose Phase 1 study in humans and tentatively identified six metabolites in addition to unchanged simufilam. Based on MS relative abundance data, unchanged simufilam was the most abundant circulating entity in AUC0-12h-pooled plasma, ranging from 69.2% to 74.9%. Of the six human metabolites identified, the N-demethylation product M245/1 was the predominant drug-related entity in AUC0-12h-pooled plasma, accounting for 19.1% to 23.8% of the total abundance.

Plasma protein binding of simufilam in mouse, rat, rabbit, dog, and human was low at ranging from 0.0 to 13.2% across all species tested. Blood to plasma partitioning showed even distribution in blood and plasma across all species tested suggesting little affinity of simufilam for either the cellular or fluid portion of the blood. Simufilam does not inhibit or induce major CYP450 enzymes, nor is a substrate or inhibitor of major human drug transporters at clinically relevant concentrations.

~~A full battery of genotoxicity studies was conducted (*in vitro* bacterial Ames, *in vitro* chromosomal aberration, and *in vivo* rat micronucleus test) and all were negative. An *in vitro* specificity screen showed no significant activation or inhibition of a panel of 68 receptors, channels and transporters.~~

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

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

AUC, respectively, over the 100 mg b.i.d. dose in subjects.

A full battery of genotoxicity studies was conducted (*in vitro* bacterial Ames, *in vitro* chromosomal aberration, and *in vivo* rat micronucleus test) and there were no mutagenic or clastogenic responses.

A 26-week oral gavage carcinogenicity study of simufilam in CByB6F1-Tg (HRAS)2Jic mice is currently in the dosing phase, while a 104-week oral gavage carcinogenicity study of simufilam in rats started dosing in February 2022 and is currently in the reporting phase.

The drug substance impurity CML 1497 was qualified for safe clinical use in a 13-week repeat dose oral toxicity study in the rat and in in vitro genetic toxicity studies. A metabolite in safety testing (MIST) study evaluated the relative exposure of circulating human plasma metabolites to rat plasma metabolites based on peak area ratios. All six metabolites identified in human plasma were identified in the rat and adequate coverage based on peak area ratio ($AUC_{rat}/AUC_{human} \geq 0.5$) was demonstrated in the rat.

More information can be found in the Investigator's Brochure.

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

2.3 Clinical Studies

Updated: In a 28-day phase 2a study (PTI-125-03), 13 subjects with mild-to-moderate AD received simufilam 100 mg b.i.d. as oral tablets. Subjects had Mini-Mental State Exam (MMSE) scores ≥ 16 and ≤ 24 and were age 50-85 with a CSF total tau/$A\beta_{42}$ ratio ≥ 0.30. ~~A second CSF sample was collected on Day 28, allowing assessment of change from baseline in biomarkers using commercial ELISA kits. All 8 biomarkers that are elevated in AD were significantly reduced from baseline (**Fig. 1**).[4] $A\beta_{42}$, which is low in AD, was increased slightly but non-significantly. Reduced inflammatory cytokines and YKL-40 indicated reduced neuroinflammation. A reduced neurodegenerative drive was suggested by reductions in neurogranin, neurofilament light chain, and total tau. The robust reduction in phospho-tau (P-Tau181) confirms the mechanism of action of simufilam~~. Simufilam was safe and well tolerated in all subjects.

A phase 2b randomized, placebo-controlled clinical study (PTI-125-02) of simufilam 50 or 100 mg tablets or placebo (1:1:1) enrolled 64 mild-to-moderate AD subjects with MMSE 16-28~~6~~.

~~Both 50 and 100 mg doses significantly improved eleven CSF biomarkers of AD pathology, neurodegeneration, neuroinflammation and blood-brain barrier integrity (**Fig. 2**). CSF biomarker analyses were conducted blind to treatment and timepoint by an outside lab, and screening and Day 28 samples for each subject were measured in triplicate in the same ELISA plates. Albumin and immunoglobulin G (IgG) were measured by immunoblotting and quantified by densitometric quantitation. These data suggest disease modification and replicate Phase 2a results in a well-controlled study.~~

~~The secondary endpoints in the phase 2b study were two cognitive measures using the Cambridge Neuropsychological Test Automated Battery. Subjects were assessed on the Paired Associate~~

~~Learning (PAL) test, measuring episodic memory, and a test of spatial working memory. The primary outcome measure for each was total errors, with errors imputed for more difficult levels not reached. Simufilam produced encouraging mean improvements from baseline on each test for both doses, suggesting cognitive enhancement (**Fig. 3**). Subjects who showed no detectable simufilam in plasma or ≥25% noncompliance by pill counts were excluded from cognitive data (5 subjects), and for episodic memory only, the most and least impaired subjects were removed by baseline score. Cognitive enhancement by simufilam is supported by preclinical data showing improved function of α7nAChR, NMDAR and insulin receptors and improved synaptic plasticity in 3xTg AD mice and in postmortem human AD brain tissue.~~

~~In both phase 2 clinical studies~~Similar to the phase 2a study, simufilam was safe and well tolerated and no subjects discontinued due to AEs.

PTI-125-04 ~~is~~ was a 12-month, open-label phase 2b safety study of simufilam followed by a 6-month randomized withdrawal and then an additional 6 months of open-label simufilam administration in mild-to-moderate Alzheimer's disease subjects. Subject participation ~~in the full 24-month study will end~~ was completed 4Q2023. Open-label adverse event data from this study is summarized in the Investigator's Brochure.

There are ~~four~~ three ongoing Phase 2 or 3 clinical studies:

> PTI-125-09 is an ~~96-week,~~ open-label extension of the PTI-125-04 study evaluating the safety and long-term treatment of simufilam in mild-to-moderate Alzheimer's disease subjects. Enrollment began 2Q2022 and is only available to subjects who have completed the 24-month PTI-125-04 study.

3. STUDY OBJECTIVES

Updated: The primary objective of this open-label extension study is to evaluate the long-term safety and tolerability of twice daily simufilam 100 mg tablets in subjects who completed one of the two double-blind simufilam phase 3 studies or who already completed participation through Week 52 in PTI-125-10.

4. SUMMARY OF STUDY DESIGN

Updated: This is a multi-national, multi-center, fixed-dose, ~~52-week,~~ open-label extension study that will continue through FDA approval of simufilam or program termination (Appendix A). After completing participation in either PTI-125-06 or PTI-125-07, subjects will have the option to participate in this study. After the subject provides consent and the Investigator confirms the subject satisfies both inclusion and exclusion (I/E) criteria, the study drug will be administered at the research site on Study Day 1 and subsequent visits will be scheduled.

Added: Subjects who already completed participation through Week 52 in PTI-125-10 will have the option to return to the study and continue participation. After the subject provides consent, the Investigator will confirm that the subject continues to satisfy both the I/E criteria. The study drug will be administered at the research site on Re-entry Day 1 and subsequent visits will be scheduled. The length of their participation gap will dictate which visits apply to them.

We anticipate up to 1,~~8~~350 subjects may enroll in this study. Approximately 170 clinical sites in the USA, Canada, the Republic of Korea, and Australia will have the option to participate in this collaborative research effort.

Updated: ~~An~~ Additional blood samples will be taken on Study Day 1 to assess Hemoglobin A1c (HbA1c) and plasma biomarkers upon receipt of required supplies. All subjects will return in 4 weeks and then every 12 weeks thereafter for safety assessments.

For subjects re-entering the study, the length of their participation gap will determine their need for clinical and laboratory assessments. A blood sample will be taken to assess HbA1c and plasma biomarkers upon receipt of required supplies.

At all post-baseline visits, subjects will report any adverse events since their last visit. In addition to adverse event monitoring, safety will be evaluated ~~at every visit~~ by vital signs, brief examinations, clinical laboratory tests (biochemistry, hematology, and urinalysis) and the Columbia Suicide Severity Rating Scale (C-SSRS). Cognition and function will be monitored using the clinical dementia rating (CDR) scale.

5.1 STUDY POPULATION

Updated: Up to 1,~~8~~350 subjects will be enrolled in the study.

5.2 INCLUSION CRITERIA

Updated: 1. Completed participation in either of the two double-blind simufilam phase 3 studies (PTI-125-06 or PTI-125-07) or Week 52 in PTI-125-10 (for subjects re-entering the study).

Updated: 4. MMSE score ≥ 11 at the PTI-125-07 Week 52 or PTI-125-06 Week 76 visit (for new PTI-125-10 participants at Study Day 1).

5.3 EXCLUSION CRITERIA

Updated: 6. Any diagnosed ~~malignant tumor~~ malignancy in the preceding phase 3 study, or since previous study participation concluded in PTI-125-10, unless approved by the Medical Monitor.

Updated: 10. An unstable medical condition that is clinically significant in the judgment of the Investigator, including significant neurologic, hepatic, renal, endocrinologic, cardiovascular, gastrointestinal, pulmonary, hematologic, immunologic or metabolic disease. For participants that re-enter the study, any significant illness or hospitalization that occurred during the gap period must be discussed with the medical monitor to confirm eligibility.

Added: 13. Medications that in the Investigator's opinion may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform cognitive testing or other study procedures should be discussed with the medical monitor.

7. STUDY PROCEDURES

Updated: Appendix B presents the Schedule of Activities for New/Active Participants. Appendix C presents the Schedule of Activities for Re-Entry Participants.

7.1.1. Study Day 1 (Dosing Initiation)

Updated as follows:

- Height (~~on Study Day 1 only,~~ to facilitate BMI calculation)
- Collect samples for HbA1c and plasma biomarkers
- Review of ~~Inclusion and Exclusion~~ I/E criteria following all Study Day 1 assessments and prior to dosing.

Added: CDR

Added: **7.1.2. Re-entry Day 1 (Dosing Re-initiation)**
This visit applies to all subjects who completed their original participation in the PTI-125-10 study and want to resume study participation. Subjects will come to the clinic in the morning whenever possible. Prior to dosing, the following will be completed:

- Informed Consent
- Medical History- focused on any new conditions that occurred during the gap period between study completion and study re-entry
- Adverse event monitoring
- Use of concomitant medications
- Vital signs (blood pressure [supine], temperature and pulse)
- Brief physical and neurologic examination
- Height
- Weight
- 12-lead resting ECG (5-min supine) - only for subjects who completed their PTI-125-10 Week 52 visit >60 days prior to re-entry
- Clinical laboratory tests (biochemistry, hematology, and urinalysis) - only for subjects who completed their PTI-125-10 Week 52 visit >60 days prior to re-entry
- Collect samples for HbA1c and plasma biomarkers
- CDR - only for subjects who completed their PTI-125-10 Week 52 visit >60 days prior to re-entry
- C-SSRS – Since Last Visit version
- Review of I/E criteria following all Re-entry Day 1 assessments and prior to dosing.

Once all Re-entry Day 1 procedures are completed, a 188-count bottle of study drug to be dispensed is assigned by the computer-based study management system.

Subjects will be administered one (1) tablet of study drug at the clinic at least 1 hour before departure. The subject will be discharged with their supply of study drug. The study partner will be instructed to administer study drug twice daily with or without food. The study partner should

be advised that a dose can be up to 4 hours late, but, if a dose is missed, the next dose should NOT be doubled.

For all follow-up visits, subjects will be instructed to bring their study drug bottle to the clinic. Research staff will conduct and log the pill count, and a new bottle of study drug will be dispensed when required.

Changed: **7.1.2. Weeks 4, 16, 28 and 40 Follow-up Visits**
Changed to: **7.1.3. Week 4 and Re-entry Week 4**

While the Week 4 visit is required for all newly enrolled participants, the Re-entry Week 4 visit applies only to re-entry subjects whose gap period between previous and current participation is >60 days. Subjects will return to clinic for these scheduled visits within a ± 5-day "window." ~~A 188-count bottle of study drug to be dispensed is assigned by the computer-based study management system.~~ The following will be completed:

- Adverse event monitoring
- Use of concomitant medications
- Vital signs (blood pressure [supine], temperature and pulse)
- Brief physical and neurologic examination
- Height
- Weight
- ~~Collect sample for HbA1c at Week 28 only~~
- 12-lead resting ECG (5-min supine) ~~at Weeks 4 and 28~~
- Clinical laboratory tests (biochemistry, hematology, and urinalysis) ~~at Weeks 4 and 28~~
- C-SSRS – Since Last Visit version
- Receive and count remaining tablets in each ~~returned~~ bottle of investigational product to assess adherence to BID dosing.

For Week 4 visits only, a 188-count bottle of study drug to be dispensed is assigned by the computer-based study management system. For Re-entry Week 4, the bottle that was previously dispensed at Re-entry Day 1, will be returned to the subject following study drug accountability.

Added: **7.1.4. Weeks 16, 40, and Repeat Visit A**
Added: Subjects will return to clinic for these scheduled visits within a ± 5-day "window." The following will be completed:

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

- Height
- Weight
- C-SSRS – Since Last Visit version
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

A 188-count bottle of study drug to be dispensed is assigned by the computer-based study management system.

Added: **7.1.5. Weeks 28, 52, and Repeat Visit B**
Added: Subjects will return to clinic for these scheduled visits within a ± 5-day "window." The following will be completed:

- Adverse event monitoring
- Use of concomitant medications
- Vital signs (blood pressure [supine], temperature and pulse)
- Brief physical and neurologic examination
- Height
- Weight
- 12-lead resting ECG (5-min supine)
- Clinical laboratory tests (biochemistry, hematology, and urinalysis)
- Collect samples for HbA1c (only if collected at the original Study Day 1 visit or on Re-entry Day 1) and plasma biomarkers
- CDR
- C-SSRS – Since Last Visit version
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

A 188-count bottle of study drug to be dispensed is assigned by the computer-based study management system

Changed: **7.1.3. Week 52 End-of-Treatment Visit / Early Termination (ET) Visit**
Changed to: **7.1.6. ~~Week 52~~ End-of-Treatment Visit / Early Termination (ET) Visit**

7.1.6. End-of-Treatment Visit (EoT) / Early Termination (ET) Visit

Added: Height

Added: Collect Samples for HbA1c (only if collected at the original Study Day 1 visit or on Re-entry Day 1) and plasma biomarkers

Added: CDR (End of Treatment visit only)

Changed: **7.1.4. Week 53-54 End-of-Study Follow-up**
Changed to: **7.1.7. End of Study Follow-up Phone Call**

7.1.9 Stopping Criteria

Updated: Bodyweight loss of ≥ 2 kg from Study Day 1 resulting in a BMI < 18.5 is an additional stopping criterion. (Note: BMI at any specific visit utilizes the height and weight recorded on that day ~~Study Day 1~~.)

7.2.1 Clinical Laboratory Tests

Updated: The following clinical laboratory tests will be performed on Study Day 1, as well as the Re-entry Day 1 (for select participants), Week 4, Re-entry Week 4, Week 28, Week 52, Repeat Visit B, and End of Treatment/Early Termination Follow-up visits:

- Biochemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphate, blood urea nitrogen (BUN), total bilirubin, creatinine, albumin, globulin, total protein, uric acid, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), lactose dehydrogenase (LDH). For new participants, HbA1c will be analyzed on Day 1, Week 28, Week 52, Repeat Visit B, and EoT/ET. For active participants HbA1c will be analyzed at Week 28, Week 52, Repeat Visit B, and EoT/ET only if HbA1c was collected and analyzed on Study Day 1. For re-entering participants, HbA1c is analyzed at Re-entry Day 1, Repeat Visit B, and EoT/ET.

Added. **7.2.2 Preparation of Samples for Plasma Biomarkers**

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

Added: **8. COGNITIVE ASSESSMENT**

Added: **8.1 CLINICAL DEMENTIA RATING**

Added: Washington University's CDR[2] characterizes six domains of cognitive and functional performance applicable to AD and related dementias: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The study partner is interviewed first by a qualified rater who assesses all six domains in the absence of the study subject. The subject is then interviewed by the same rater in the absence of the study partner. A CDR global score can be calculated by accessing Washington University's online algorithm (CDR® Calculator | National Alzheimer's Coordinating Center (naccdata.org)) where 0 = no dementia, and scores of 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively. The sum of boxes[3] can also be calculated by summing the six individual domain scores. This detailed quantitative general index may provide more information than the CDR global score in patients with mild dementia.

10. EARLY DISCONTIUATION

- Updated: Vital signs (blood pressure, temperature and pulse), brief physical and neurologic examination, height, weight, clinical laboratory tests, collection of HbA1c (if collected on Study Day 1 or Re-entry Day 1), plasma biomarkers, ECG, use of concomitant medications, and adverse events should be obtained at discharge prior to release.
- C-SSRS (as detailed in Section 7.1.~~36~~36 – Early Termination Visit), if not performed within the last 30 days.

11.5 SERIOUS ADVERSE EVENTS- REPORTING

Updated: ~~SAEs must be immediately reported to the responsible IRB.~~ Sites are to follow their IRB/EC requirements for reporting SAEs/AEs.

12.3 HBA1C ANALYSIS

Changed: We will analyze change from baseline in HbA1c levels at ~~Week 28 and Week 52~~ in subjects previously randomized to placebo in the PTI-125-06 or PTI-125-07 phase 3 studies. We will also compare Day 1 HbA1c values of subjects previously on placebo to those subjects previously on simufilam. All analyses will be fully described in the statistical analysis plan.

Changed To: HbA1c levels will be collected and measured repeatedly from all subjects for whom a Day 1 HbA1c has been collected (including re-entry subjects), and these data will be analyzed by a linear mixed model for repeated measurements. Two subject cohorts will be analyzed separately: those randomized to placebo in the PTI-125-06 or PTI-125-07 phase 3 studies, and those randomized to simufilam in those studies. The analytical model will be fully described in the statistical analysis plan.

Added: 12.4 PLASMA BIOMARKER ANALYSIS

Added: Plasma assays may include P-tau217, glial fibrillary acidic protein, neurofilament light, and other biomarkers. All plasma biomarker data measured repeatedly will be analyzed by linear mixed models for repeated measurements. Subject cohorts of interest for separate analyses include subjects who participated in one of the plasma biomarker sub-studies of the PTI-125-06 or PTI-125-07 phase 3 studies; subjects randomized to placebo and subjects randomized to simufilam in the aforementioned studies. Within-subject change from baseline analyses may also be conducted. The analytical model and all other analyses will be fully described in the statistical analysis plan.

Added: 12.5 CLINICAL DEMENTIA RATING

Added: CDR sum of boxes and/or global score assessments measured repeatedly will be analyzed using a linear mixed model for repeated measurements. Two subject cohorts will be analyzed separately: those randomized to placebo in the PTI-125-06 or PTI-125-07 phase 3 studies, and

those randomized to simufilam in those studies. Within-subject change from baseline may also be conducted. The analytical model and all other analyses will be fully described in the statistical analysis plan.

Added: 12.6 Interim Analysis

Added: Interim analysis of plasma biomarker and cognitive data may occur at the discretion of the sponsor.

13. STUDY TERMINATION

Updated: The study will be terminated following approval by the FDA of simufilam for the treatment of Alzheimer's disease ~~completion of the study~~ or at any time at the discretion of the Sponsor.

Updated: 16. References

~~1. Burns LH, Wang H-Y. Altered filamin A enables amyloid beta-induced tau hyperphosphorylation and neuroinflammation in Alzheimer's disease. Neuroimmunology and 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. Neurobiology of Aging 2017;55:99-114.~~

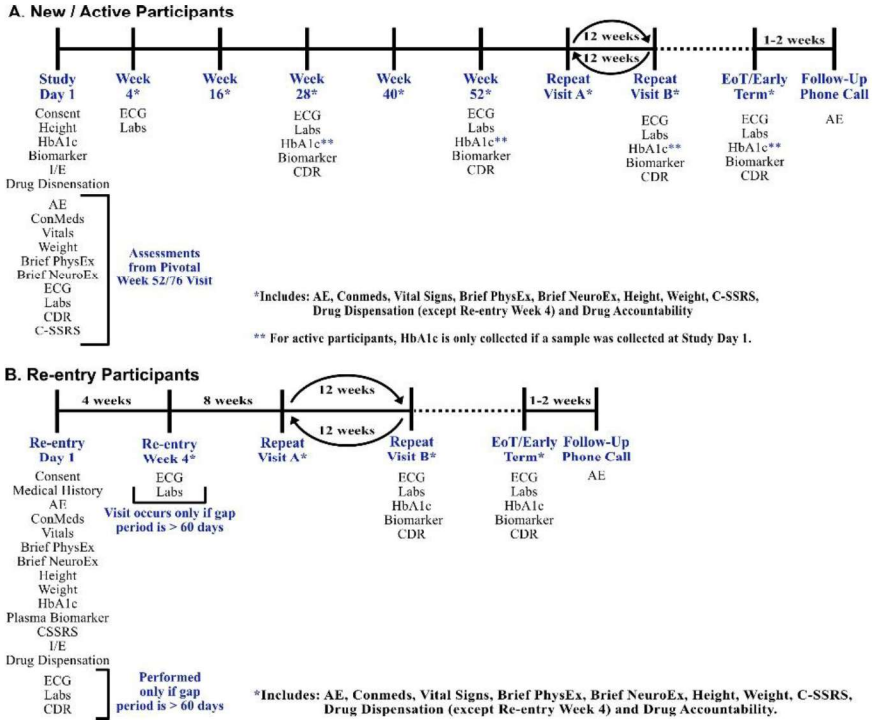
~~3. Wang H-Y, Bakshi K, Frankfurt M, et al. Reducing amyloid-related Alzheimer's disease pathogenesis by a small molecule targeting filamin A. Journal of Neuroscience 2012;32:9773-84.~~

~~4. Wang H-Y, Pei Z, K.-C. Lee K-C, et al. PTI-125 reduces biomarkers of Alzheimer's disease in patients. The Journal of Prevention of Alzheimer's Disease 2020;7:256-64~~

1. Wang, H. Y., Cecon, E., Dam, J., Pei, Z., Jockers, R., & Burns, L. H. (2023). Simufilam Reverses Aberrant Receptor Interactions of Filamin A in Alzheimer's Disease. *International journal of molecular sciences*, *24*(18), 13927. https://doi.org/10.3390/ijms241813927.
2. Morris J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, *43*(11), 2412–2414. https://doi.org/10.1212/wnl.43.11.2412-a
3. O'Bryant, S. E., Lacritz, L. H., Hall, J., Waring, S. C., Chan, W., Khodr, Z. G., Massman, P. J., Hobson, V., & Cullum, C. M. (2010). Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. *Archives of neurology*, *67*(6), 746–749. https://doi.org/10.1001/archneurol.2010.115
4. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. American Journal of Psychiatry

2011;168(12):1266-77.

Added: 17. APPENDIX A- STUDY DESIGN SCHEMATIC



18. APPENDIX B – SCHEDULE OF ACTIVITIES FOR NEW/ACTIVE PARTICIPANTS

Changed: 16. APPENDIX A – SCHEDULE OF ACTIVITIES
Changed to: 18. APPENDIX B – SCHEDULE OF ACTIVITIES FOR NEW/ACTIVE PARTICIPANTS

Changed: Week 52 ET/ED
Changed to: Wk 52

Added: Repeat Visit A

Added: Repeat Visit B

Added: EoT/Early Term

Changed: Week 53 to Week 54
Changed to: Follow-up Phone Call

Added: Height measurement at Week 4, Week 16, Week 28, Week 40, Week 52, Repeat Visit B, EoT/ET.

Added: Plasma Biomarkers collected on Study Day 1, Week 28, Week 52, Repeat Visit B, EoT/ET.

Added: CDR performed on Study Day 1, Week 28, Week 52, Repeat Visit B, EoT.

Added: [1]Plasma Biomarker collection will begin upon receipt of required supplies.

Added: Study Drug Dispensation to Week 52, Repeat Visit A, Repeat Visit B.

Added Study Drug Accountability to Week 52, Repeat Visit A, Repeat Visit B, EoT/ET.

Updated: ~~1~~[2]On Study Day 1, as well as all remaining visits, the 'C-SSRS Since Last Visit' version will be administered.

Updated: ~~2~~[3]The first dose of study drug is administered at the clinic to all subjects on Study Day 1 at least four hours after any prior dose and at least one hour before departure.

Removed: [3]~~HbA1c collection will begin upon receipt of required supplies.~~

Updated: [4]~~Week 28 and Week 52~~ HbA1c should only be collected in subjects with a Study Day 1 HbA1c.

Added: [5]Repeat Visit A occurs 12 weeks following the Week 52 visit and then reoccurs every 24 weeks thereafter.

Added: [6]Repeat Visit B occurs 12 weeks following the first Repeat Visit A visit and then reoccurs every 24 weeks thereafter.

Added: [7]CDR is only performed at the End of Treatment visit.

Added: [8]Follow-up phone call occurs 1-2 weeks after End of Treatment/Early Termination.

Added:

19. APPENDIX C – SCHEDULE OF ACTIVITIES FOR RE-ENTRY PARTICIPANTS

Procedures	Re-entry Day 1	Re-entry Wk 4[5]	Repeat Visit A[6]	Repeat Visit B[7]	EoT / Early Term	Follow-up Phone Call[9]
Informed Consent	X					
Medical History	X					
I/E Criteria	X					
Adverse Events	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	
Vital Signs	X	X	X	X	X	
Brief Physical Exam	X	X	X	X	X	

Procedures	Re-entry Day 1	Re-entry Wk 4[5]	Repeat Visit A[6]	Repeat Visit B[7]	EoT / Early Term	Follow-up Phone Call[9]
Brief Neurologic Exam	X	X	X	X	X	
Height	X	X	X	X	X	
Weight	X	X	X	X	X	
Resting ECG	X[1]	X		X	X	
Biochemistry, Hematology, Urinalysis	X[1]	X		X	X	
HbA1c	X			X	X	
Plasma Biomarkers[2]	X			X	X	
CDR	X[1]			X	X[8]	
C-SSRS[3]	X	X	X	X	X	
Study Drug Dispensation	X[4]		X	X		
Study Drug Accountability		X	X	X	X	
End of Study Follow-up Phone Call						X

[1]Resting ECG, Biochemistry, Hematology, Urinalysis, and CDR to be performed only for Re-entry Day 1 subjects who completed the PTI-125-10 Week 52 visit >60 days prior to re-entry.

[2]Plasma Biomarker collection will begin upon receipt of required supplies.

[3]On Re-entry Day 1, as well as all remaining visits, the 'C-SSRS Since Last Visit' version will be administered.

[4]The first dose of study drug is administered at the clinic to all subjects at least one hour before departure.

[5]Re-entry Week 4 visit performed only for Re-entry subjects who completed PTI-125-10 Week 52 visit >60 days prior to re-entry.

[6]Repeat Visit A occurs 12 weeks following the Re-entry Day 1 visit and then reoccurs every 24 weeks thereafter.

[7]Repeat Visit B occurs 12 weeks following the first Repeat Visit A and then reoccurs every 24 weeks thereafter.

[8]CDR is only performed at the End of Treatment visit.

[9]Follow-up phone call to occur 1-2 weeks after End of Treatment/Early Term.

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

AN OPEN-LABEL, LONG-TERM EXTENSION STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF SIMUFILAM 100 MG TABLETS IN PARTICIPANTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE

Approvals:

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Signing Time: 22-Oct-2024 | 14:06 CDT
9D60F9221DE944859AD2EE06ADD9083E

22-Oct-2024 | 14:07 CDT

James W. Kupiec, MD
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22-Oct-2024 | 15:40 CDT

Michael Marsman, PharmD
Senior Vice President, Regulatory Affairs
Cassava Sciences, Inc.

Date

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1. LIST OF ABBREVIATIONS

α7nAChR	α7 nicotinic acetylcholine receptor
$A\beta_{42}$	amyloid $beta_{1-42}$
AD	Alzheimer's disease
AE	Adverse Event
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
AUC	area under the curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CDR	Clinical Dementia Rating
CFR	Code of Federal Regulations
Cmax	maximum plasma concentration
CNS	Central Nervous System
CR	Child-Resistant
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CSI	Cassava Sciences, Inc.
C-SSRS	Columbia-Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
EDC	Electronic Data Capture
EDTA	ethylenediaminetetraacetic acid
EoT	End of Treatment
FDA	Food and Drug Administration
FLNA	filamin A
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
HbA1c	hemoglobin A1c
hERG	human ether-a-go-go-related gene
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
I/E	Inclusion/Exclusion
IR	Insulin Receptor
IRB	Independent Review Board
LAR	Legally Authorized Representative
LDH	lactose dehydrogenase
MMSE	Mini-Mental State Examination
NOAEL	no observable adverse effect level

PK	Pharmacokinetics
PTI-125	former name of simufilam
RBC	Red Blood Cell
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
ULN	Upper Limit of Normal
WBC	White Blood Cell
Wk	Week

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, through actions involving filamin A (FLNA), prevents beta amyloid$_{1-42}$ (Aβ_{42})-induced toxic signaling cascades. Aβ_{42}, in monomer or small oligomer form, hijacks the α7-nicotinic acetylcholine receptor (α7nAChR) and signals via this receptor to hyperphosphorylate tau. Simufilam disrupts the association between Aβ_{42} and the α7nAChR[1]. In addition, Aβ_{42} activates toll-like receptor 4 leading to inflammatory cytokine release and neuroinflammation. In AD mouse models, simufilam reduced cytokine release compared to control mice[1]. We therefore expect simufilam both to improve cognition and to slow AD progression.

2.2. NONCLINICAL TESTING PROGRAM

A robust nonclinical adsorption, distribution, metabolism, and excretion, safety pharmacology, general and genetic toxicology program has been conducted with simufilam. Additional nonclinical studies, including carcinogenicity studies, are ongoing. A process impurity occurring in the drug substance, CML 1497, has been fully qualified for safe clinical use; additional studies with human metabolites are currently underway.

In vitro assays and safety pharmacology studies in rat and dog showed no off-target pharmacological effects on cardiovascular systems or respiratory function, or any adverse neurobehavioral effects.

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 electrocardiogram (ECG) parameters in the dog cardiovascular study. The *in vitro* human ether-a-go-go-related gene test for cardiotoxicity also indicated no adverse effect.

PK, biodistribution, metabolism, and excretion studies were conducted to assess the bioavailability, biodistribution, mass balance, and excretion of simufilam and to determine its metabolic fate in vitro and in vivo. Oral bioavailability was high in rat and dog. Toxicokinetic studies were included in the toxicology studies to ascertain levels of systemic exposure. Rat biodistribution studies showed near 100% total mean recovery of oral dose radioactivity; urinary excretion accounted for close to 60% of the dose, with the remainder found in bile and feces. Quantitative Whole-Body Autoradiography indicated that simufilam was widely distributed to tissues. The metabolite radioprofiling and identification phase of the mass balance and PK study in rats indicated that simufilam was extensively metabolized in the rat and metabolites were excreted in urine, bile and feces.

Elimination was rapid but incomplete at 24 hours.

An exploratory metabolite searching, identification, and relative abundance determination was conducted on plasma samples from a 5-Day multiple dose Phase 1 study in humans and tentatively identified six metabolites in addition to unchanged simufilam. Based on MS relative abundance data, unchanged simufilam was the most abundant circulating entity in AUC0-12h-pooled plasma, ranging from 69.2% to 74.9%. Of the six human metabolites identified, the N-demethylation product M245/1 was the predominant drug-related entity in AUC0-12h-pooled plasma, accounting for 19.1% to 23.8% of the total abundance.

Plasma protein binding of simufilam in mouse, rat, rabbit, dog, and human was low at ranging from 0.0 to 13.2% across all species tested. Blood to plasma partitioning showed even distribution in blood and plasma across all species tested suggesting little affinity of simufilam for either the cellular or fluid portion of the blood. Simufilam does not inhibit or induce major CYP450 enzymes, nor is a substrate or inhibitor of major human drug transporters at clinically relevant concentrations.

Simufilam has been tested in single dose and repeat dose oral toxicity studies of up to 6 months in rats and 9 months in dogs. An initial 6-month repeat dose oral toxicity study in rats (with simufilam dosed at 50, 500 and 1000 mg/kg/day), indicated a toxicological response characterized by decreased body weights and adverse structural and functional alterations in the liver at500 and 1000 mg/kg/day, including increased hepatic weight, hepatocellular hypertrophy and vacuolation, single/multiple basophilic/ eosinophilic/clear cell focus, hepatocellular degeneration, pigmentation, and oval cell hyperplasia. The presence of bile pigment was consistent with cholestasis. These findings correlated with changes to the clinical chemistry profile, including increased ALP and total/direct bilirubin. A 1-month recovery period showed complete recovery of the hepatocellular degeneration and partial recovery of hepatocellular hypertrophy; other microscopic findings in the liver remained. The no observable effect level (NOAEL) in this 6-month study was 50 mg/kg/day, corresponding to a safety margin of 6- and 1.6-fold based on C_{max} and AUC over the 100 mg b.i.d. dose in human subjects. A second 6-month repeat dose oral toxicity study in rats with simufilam at 125 and 250 mg/kg/day determined the 6-month NOAEL in the rat to be < 125 mg/kg/day, based on hepatocellular vacuolation in both sexes and hepatocellular hypertrophy in females at 125 and 250 mg/kg. Additional studies are ongoing to evaluate whether these liver effects are rat specific.

A 9-month toxicity study in dogs, a NOAEL of simufilam at 75 mg/kg. The high dose of 200 mg/kg/day was decreased to 150 mg/kg/day after 1 month due to bodyweight loss considered unsustainable for a 9-month study. Clinical signs were slight hypoactivity and incidences of slight muscle fasciculations early in the study, and salivation. There were no pathology findings, but the high dose was considered adverse due to two unexplained

deaths. The 75 mg/kg/day NOAEL provides 38- and 19-fold safety margins based on C_{max} and AUC over the 100 mg b.i.d. dose in subjects.

A full battery of genotoxicity studies was conducted (*in vitro* bacterial Ames, *in vitro* chromosomal aberration, and *in vivo* rat micronucleus test) and there were no mutagenic or clastogenic responses.

A 26-week oral gavage carcinogenicity study of simufilam in CByB6F1-Tg (HRAS)2Jic mice is currently in the dosing phase, while a 104-week oral gavage carcinogenicity study of simufilam in rats started dosing in February 2022 and is currently in the reporting phase.

The drug substance impurity CML 1497 was qualified for safe clinical use in a 13-week repeat dose oral toxicity study in the rat and in in vitro genetic toxicity studies. A metabolite in safety testing (MIST) study evaluated the relative exposure of circulating human plasma metabolites to rat plasma metabolites based on peak area ratios. All six metabolites identified in human plasma were identified in the rat and adequate coverage based on peak area ratio ($AUC_{rat}/AUC_{human} \geq 0.5$) was demonstrated in the rat.

More information can be found in the Investigator's Brochure.

2.3. CLINICAL STUDIES

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

In a 28-day phase 2a study (PTI-125-03), 13 subjects with mild-to-moderate AD received simufilam 100 mg b.i.d. as oral tablets. Subjects had Mini-Mental State Exam (MMSE) scores ≥ 16 and ≤ 24 and were age 50-85 with a CSF total tau/$A\beta_{42}$ ratio ≥ 0.30. Simufilam was safe and well tolerated in all subjects.

A phase 2b randomized, placebo-controlled clinical study (PTI-125-02) of simufilam 50 or 100 mg tablets or placebo (1:1:1) enrolled 64 mild-to-moderate AD subjects with MMSE 16-28. Similar to the phase 2a study, simufilam was safe and well tolerated and no subjects discontinued due to AEs.

PTI-125-04 was a 12-month, open-label phase 2b safety study of simufilam followed by a 6-month randomized withdrawal and then an additional 6 months of open-label simufilam administration in mild-to-moderate Alzheimer's disease subjects. Subject participation was

completed in 4Q2023. Open-label adverse event data from this study is summarized in the Investigator's Brochure.

There are three ongoing Phase 2 or 3 clinical studies:

PTI-125-09 is an open-label extension of the PTI-125-04 study evaluating the safety and long-term treatment of simufilam in mild-to-moderate Alzheimer's disease subjects. Enrollment began 2Q2022 and is only available to subjects who have completed the 24-month PTI-125-04 study.

PTI-125-06 is a phase 3, randomized, double-blind, 3-arm, 76-week study investigating the safety and efficacy of 50 mg and 100 mg of simufilam, twice daily, versus placebo in slowing cognitive and functional decline in approximately 1,083 subjects with mild-to-moderate Alzheimer's disease. The assessment of neuropsychiatric symptom emergence and the impact of simufilam on CSF biomarkers represent key secondary objectives. The study is also evaluating plasma and imaging biomarkers in a series of optional sub-studies.

PTI-125-07 is a phase 3, randomized, double-blind, 2-arm, 52-week study investigating the safety and efficacy of 100 mg of simufilam, twice daily, versus placebo in slowing cognitive and functional decline in approximately 750 subjects with mild-to-moderate Alzheimer's disease. The assessment of neuropsychiatric symptom emergence is a key secondary objective. The study is also evaluating the impact of simufilam on plasma biomarkers in an optional sub-study.

3. STUDY OBJECTIVES

The primary objective of this open-label extension study is to evaluate the long-term safety and tolerability of twice daily simufilam 100 mg tablets in subjects who completed one of the two double-blind simufilam phase 3 studies or who already completed participation through Week 52 in PTI-125-10.

4. SUMMARY OF STUDY DESIGN

This is a multi-national, multi-center, fixed-dose, open-label extension study that will continue through FDA approval of simufilam or program termination (Appendix A). After completing participation in either PTI-125-06 or PTI-125-07, subjects will have the option to participate in this study. After the subject provides consent and the Investigator confirms the subject satisfies both inclusion and exclusion (I/E) criteria, the study drug will be administered at the research site on Study Day 1 and subsequent visits will be scheduled.

Subjects who already completed participation through Week 52 in PTI-125-10 will have the option to return to the study and continue participation. After the subject provides consent, the Investigator will confirm that the subject continues to satisfy both the I/E

criteria. The study drug will be administered at the research site on Re-entry Day 1 and subsequent visits will be scheduled. The length of their participation gap will dictate which visits apply to them.

We anticipate up to 1,350 subjects may enroll in this study. Approximately 170 clinical sites in the USA, Canada, the Republic of Korea, and Australia will have the option to participate in this collaborative research effort.

For subjects electing to participate, the clinical and laboratory assessments from the Week 76 (PTI-125-06) or Week 52 (PTI-125-07) End-of-Treatment visit will serve as Baseline Visit assessments for the open-label study on Study Day 1. Additional blood samples will be taken on Study Day 1 to assess Hemoglobin A1c (HbA1c) and plasma biomarkers upon receipt of required supplies. All subjects will return in 4 weeks and then every 12 weeks thereafter for safety assessments.

For subjects re-entering the study, the length of their participation gap will determine their need for clinical and laboratory assessments. A blood sample will be taken to assess HbA1c and plasma biomarkers upon receipt of required supplies.

At all post-baseline visits, subjects will report any adverse events since their last visit. In addition to adverse event monitoring, safety will be evaluated by vital signs, brief examinations, clinical laboratory tests (biochemistry, hematology, and urinalysis) and the Columbia Suicide Severity Rating Scale (C-SSRS). Cognition and function will be monitored using the Clinical Dementia Rating (CDR) scale. Study drug use since the last visit will be assessed and a new bottle of study drug will be dispensed.

The emerging subject safety assessments from this study will be monitored on an ongoing basis by an independent Data Safety Monitoring Board (DSMB) throughout its duration.

5. SUBJECT SELECTION

5.1. STUDY POPULATION

Up to 1,350 subjects will be enrolled in the study.

5.2. INCLUSION CRITERIA

Each subject must meet the following Inclusion Criteria:

1. Completed participation in either of the two double-blind simufilam phase 3 studies (PTI-125-06 or PTI-125-07) or Week 52 in PTI-125-10 (for subjects re-entering the study).

2. Capable of providing either written informed consent or, if incapable of written consent, permission to participate can be obtained from a Legally Authorized Representative (LAR). Verbal assent to the study procedures and schedule is required of all participants. If, in the Investigator's judgment, a subject loses capacity to consent during the duration of the study, an LAR must consent on behalf of the subject. All consent processes must be undertaken prior to any study procedures.
3. Clinical presentation continues to be consistent with Alzheimer's disease.
4. MMSE score ≥ 11 at the PTI-125-07 Week 52 or PTI-125-06 Week 76 visit (for new PTI-125-10 participants at Study Day 1).
5. Male subjects must be willing to continue use of contraception during the study. With female partners of childbearing potential, male subjects, regardless of their fertility status, must agree to either remain abstinent or use condoms in combination with one additional highly effective method of contraception (e.g., oral or implanted contraceptives, or intrauterine devices) or an effective method of contraception (e.g., diaphragms with spermicide or cervical sponges) during the study and for 14 days after study drug dosing has been completed.
6. Fluency in a language of the research site and the utilized assessment materials.
7. Continues to have adequate visual and auditory acuity (in the Investigator's judgment) that is sufficient to complete all scheduled assessments (eyeglasses and hearing aids are permitted).
8. Fully vaccinated against COVID-19.
9. Availability of a person (a study partner) who, in the Investigator's opinion, has frequent and sufficient contact with the study subject (defined as ≥ 10 hours per week), and can:
    a. provide accurate information regarding the study subject's cognitive and functional abilities,
    b. agree to comply with and participate at all scheduled visits and study procedures,
    c. sign the necessary consent form,
    d. maintain the same level of interaction with the study subject throughout the study duration.

5.3. EXCLUSION CRITERIA

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

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

2. Evidence of a neurologic condition other than AD that, in the judgment of the Investigator, significantly contributes to the subject's dementia. This may include, but is not limited to, frontotemporal dementia, dementia with Lewy bodies, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, Huntington's disease, or normal pressure hydrocephalus.
3. Subjects with any current, clinically significant psychiatric diagnosis other than AD if, in the judgment of the Investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug safety or affect the subject's ability either to comply with study procedures or to complete the study.
4. New diagnosis of severe major depression even without psychotic features.
5. Significant risk for suicide. Affirms suicidal ideation in response to questions number 4 or 5 in the C-SSRS during the past 3 months (i.e., "active suicidal ideation with some intent to act, without specific plan," or "active suicidal ideation with specific plan and intent") or affirms any of the questions contained in the Suicidal Behavior section of the C-SSRS as applicable during the past 12 months.
6. Any diagnosed malignancy in the preceding phase 3 study or since previous study participation concluded in PTI-125-10, unless approved by the Medical Monitor.
7. The subject has experienced a serious adverse event during the preceding phase 3 study that presents an increased safety risk during this open-label extension study.
8. The subject has a moderate or severe ongoing adverse event from the preceding phase 3 study considered a potential safety risk in the judgment of the Investigator.
9. Clinically significant abnormality in the past 90 days on any clinical laboratory test that could impact safety in the judgment of the Investigator.
10. An unstable medical condition that is clinically significant in the judgment of the Investigator, including significant neurologic, hepatic, renal, endocrinologic, cardiovascular, gastrointestinal, pulmonary, hematologic, immunologic or metabolic disease. For participants that re-enter the study, any significant illness or hospitalization that occurred during the gap period must be discussed with the medical monitor to confirm eligibility.
11. Any other medical or neurological condition (other than Alzheimer's disease), that, in the opinion of the Investigator, might represent a contributing cause to the subject's cognitive impairment, or affect subject safety, ability to comply with study assessments, drug compliance and completion of the study.
12. Use of aducanumab, lecanemab, or any anti-amyloid monoclonal antibody.
13. Medications that in the Investigator's opinion may contribute to cognitive impairment, put the subject at higher risk for AEs, or impair the subject's ability to perform

cognitive testing or other study procedures should be discussed with the medical monitor.

6. STUDY DRUG

6.1. SIMUFILAM PHYSICAL DESCRIPTION AND PREPARATION

Investigational simufilam (100 mg active strength) will be supplied by Cassava as coated oral tablets.

6.1.1. Packaging and Labelling

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

Each bottle is open-labeled and includes a unique Medication ID number that is referenced for dispensing investigational drug. A computer-based clinical study management system will specify the Medication ID number to be dispensed to the subject at clinical visits.

6.1.2. Storage

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

6.1.3. Drug Accountability

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

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

6.2. ADMINISTRATION AND DOSING REGIMEN

Subjects will receive 100 mg simufilam tablets for twice daily (b.i.d.) oral administration. Study drug can be taken with or without food.

6.3. CONCOMITANT MEDICATIONS

Use of prescription or non-prescription medications will be recorded during the study.

7. STUDY PROCEDURES

Appendix B presents the Schedule of Activities for New/Active Participants. Appendix C presents the Schedule of Activities for Re-Entry Participants.

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

7.1. EVALUATIONS BY VISIT

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

7.1.1. Study Day 1 (Dosing Initiation)

The clinical and laboratory assessments performed at the Week 76 (PTI-125-06) or Week 52 (PTI-125-07) End-of-Treatment visit will serve as the baseline (Study Day 1) for this open-label extension study. Subjects will come to the clinic in the morning whenever possible. Prior to dosing, the following will be completed:

- Informed Consent
- Height (to facilitate BMI calculation)
- Collect samples for HbA1c and plasma biomarkers
- Review of I/E criteria following all Study Day 1 assessments and prior to dosing.

From the Week 76 or Week 52 End-of-Treatment visit (PTI-125-06 or PTI-125-07, respectively) in the phase 3 study in which the subject participated:

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

- Clinical laboratory tests (biochemistry, hematology, and urinalysis)
- 12-lead resting ECG (5-min supine)
- CDR

If the Study Day 1 (baseline) visit does not coincide with the Week 76 or Week 52 End-of-Treatment visit for the double-blind study (PTI-125-06 or PTI-125-07, respectively), the Investigator should confer with the Medical Monitor to determine whether selected assessments may need to be repeated.

Once all Study Day 1 procedures and assessments have been completed, the 70-count bottle of study drug to be dispensed is assigned by the computer-based study management system.

Subjects will be administered one (1) tablet of study drug at the clinic at least 4 hours after any prior dose and at least 1 hour before departure. The subject will be discharged with their supply of study drug. The study partner will be instructed to administer study drug twice daily with or without food. The study partner should be advised that a dose can be up to 4 hours late, but, if a dose is missed, the next dose should NOT be doubled.

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

For all follow-up visits, subjects will be instructed to bring their study drug bottle to the clinic. Research staff will conduct and log the pill count, and a new bottle of study drug will be dispensed.

7.1.2. Re-entry Day 1 (Dosing Re-initiation)

This visit applies to all subjects who completed their original participation in the PTI-125-10 study and want to resume study participation. Subjects will come to the clinic in the morning whenever possible. Prior to dosing, the following will be completed:

- Informed Consent
- Medical History- focused on any new conditions that occurred during the gap period between study completion and study re-entry
- Adverse event monitoring
- Use of concomitant medications
- Vital signs (blood pressure [supine], temperature and pulse)
- Brief physical and neurologic examination
- Height

- Weight
- 12-lead resting ECG (5-min supine) - only for subjects who completed their PTI-125-10 Week 52 visit >60 days prior to re-entry
- Clinical laboratory tests (biochemistry, hematology, and urinalysis) - only for subjects who completed their PTI-125-10 Week 52 visit >60 days prior to re-entry
- Collect samples for HbA1c and plasma biomarkers
- CDR - only for subjects who completed their PTI-125-10 Week 52 visit >60 days prior to re-entry
- C-SSRS – Since Last Visit version
- Review of I/E criteria following all Re-entry Day 1 assessments and prior to dosing.

Once all Re-entry Day 1 procedures are completed, a 188-count bottle of study drug to be dispensed is assigned by the computer-based study management system.

Subjects will be administered one (1) tablet of study drug at the clinic at least 1 hour before departure. The subject will be discharged with their supply of study drug. The study partner will be instructed to administer study drug twice daily with or without food. The study partner should be advised that a dose can be up to 4 hours late, but, if a dose is missed, the next dose should NOT be doubled.

For all follow-up visits, subjects will be instructed to bring their study drug bottle to the clinic. Research staff will conduct and log the pill count, and a new bottle of study drug will be dispensed when required.

7.1.3. Week 4 and Re-entry Week 4

While the Week 4 visit is required for all newly enrolled participants, the Re-entry Week 4 visit applies only to re-entry subjects whose gap period between previous and current participation is >60 days. Subjects will return to clinic for these scheduled visits within a ± 5-day "window." The following will be completed:

- Adverse event monitoring
- Use of concomitant medications
- Vital signs (blood pressure [supine], temperature and pulse)
- Brief physical and neurologic examination
- Height
- Weight
- 12-lead resting ECG (5-min supine)

- Clinical laboratory tests (biochemistry, hematology, and urinalysis)
- C-SSRS – Since Last Visit version
- Receive and count remaining tablets in each bottle of investigational product to assess adherence to BID dosing.

For Week 4 visits only, a 188-count bottle of study drug to be dispensed is assigned by the computer-based study management system. For Re-entry Week 4, the bottle that was previously dispensed at Re-entry Day 1, will be returned to the subject following study drug accountability.

7.1.4. Weeks 16, 40, and Repeat Visit A

Subjects will return to clinic for these scheduled visits within a ± 5-day "window." The following will be completed:

- Adverse event monitoring
- Use of concomitant medications
- Vital signs (blood pressure [supine], temperature and pulse)
- Brief physical and neurologic examination
- Height
- Weight
- C-SSRS – Since Last Visit version
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

A 188-count bottle of study drug to be dispensed is assigned by the computer-based study management system.

7.1.5. Weeks 28, 52, and Repeat Visit B

Subjects will return to clinic for these scheduled visits within a ± 5-day "window." The following will be completed:

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

- Weight
- 12-lead resting ECG (5-min supine)
- Clinical laboratory tests (biochemistry, hematology, and urinalysis)
- Collect samples for HbA1c (only if collected at the original Study Day 1 visit or on Re-entry Day 1) and plasma biomarkers
- CDR
- C-SSRS – Since Last Visit version
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

A 188-count bottle of study drug to be dispensed is assigned by the computer-based study management system

7.1.6. End-of-Treatment Visit (EoT) / Early Termination (ET) Visit

Subjects will return to clinic for this scheduled visit within a ± 5-day "window." The following will be completed:

- Adverse event monitoring
- Use of concomitant medications
- Vital signs (blood pressure [supine], temperature and pulse)
- Brief physical and neurologic examination
- Height
- Weight
- 12-lead resting ECG (5-min supine)
- Clinical laboratory tests (biochemistry, hematology, and urinalysis)
- Collect samples for HbA1c (only if collected at the original Study Day 1 visit or on Re-entry Day 1) and plasma biomarkers
- CDR (End of Treatment visit only)
- C-SSRS – Since Last Visit version
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

7.1.7. End-of-Study Follow-up Phone Call

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

scheduled.

7.1.8. Unscheduled Visits and Discontinuation due to AEs

For unscheduled visits due to AEs, any assessments conducted will be at the discretion of the Investigator and pertinent to the AE. If a decision is made to discontinue the subject from study drug, the Sponsor will be notified immediately. The subject should be followed and treated by the Investigator until the AE has resolved or stabilized (see Section 10 – Adverse Events). Restarting the subject on study drug will be a mutual decision by the Investigator and the Sponsor. See also Section 9 – Early Discontinuation.

7.1.9. Stopping Criteria

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

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

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

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

management.

Bodyweight loss of ≥ 2 kg from Study Day 1 resulting in a BMI < 18.5 is an additional stopping criterion. (Note: BMI at any specific visit utilizes the height and weight recorded on that day.)

7.2. LABORATORY ASSESSMENTS

7.2.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed on Study Day 1, as well as the Re-entry Day 1 (for select participants), Week 4, Re-entry Week 4, Week 28, Week 52, Repeat Visit B, and End of Treatment/Early Termination Follow-up visits:

- Biochemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphate, blood urea nitrogen (BUN), total bilirubin, creatinine, albumin, globulin, total protein, uric acid, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), lactose dehydrogenase (LDH). For new participants, HbA1c will be analyzed on Day 1, Week 28, Week 52, Repeat Visit B, and EoT/ET. For active participants HbA1c will be analyzed at Week 28, Week 52, Repeat Visit B, and EoT/ET only if HbA1c was collected and analyzed on Study Day 1. For re-entering participants, HbA1c is analyzed at Re-entry Day 1, Repeat Visit B, and EoT/ET.
- Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count.
- Urinalysis: color, specific gravity, pH, protein, glucose, ketones, occult blood, nitrites and leukocyte esterase. A "reflex" microscopic examination will be performed if protein, occult blood, nitrites or leukocyte esterase is present on the basic analysis.

7.2.2. Preparation of Samples for Plasma Biomarkers

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

8. COGNITIVE ASSESSMENT

8.1. CLINICAL DEMENTIA RATING SCALE

Washington University's CDR[2] characterizes six domains of cognitive and functional

performance applicable to AD and related dementias: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The study partner is interviewed first by a qualified rater who assesses all six domains in the absence of the study subject. The subject is then interviewed by the same rater in the absence of the study partner. A CDR global score can be calculated by accessing Washington University's online algorithm (CDR® Calculator | National Alzheimer's Coordinating Center (naccdata.org)) where 0 = no dementia, and scores of 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively. The sum of boxes[3] can also be calculated by summing the six individual domain scores. This detailed quantitative general index may provide more information than the CDR global score in patients with mild dementia.

9. SAFETY ASSESSMENTS

9.1. COLUMBIA-SUICIDE SEVERITY RATING SCALE

The C-SSRS[4] is an assessment tool used to assess the lifetime suicidality of a subject (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS Since Last Visit).

10. EARLY DISCONTINUATION

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

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

- The reason for early study discontinuation. If the subject is withdrawn for more than one reason, each reason should be documented in the source documents and the most clinically relevant reason should be entered on the CRF.
- Vital signs (blood pressure, temperature, and pulse), brief physical and neurologic examination, height, weight, clinical laboratory tests, collection of HbA1c (if collected on Study Day 1 or Re-entry Day 1), plasma biomarkers, ECG, use of concomitant medications, and adverse events should be obtained at discharge prior to release.
- C-SSRS (as detailed in Section 7.1.6 – Early Termination Visit), if not performed within the last 30 days.

11. ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

11.1. ADVERSE EVENTS – DEFINITION

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

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

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

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

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

11.2. ADVERSE EVENTS – SEVERITY RATING

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

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

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

11.3. ADVERSE EVENTS – RELATIONSHIP TO STUDY DRUG

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

11.4. SERIOUS ADVERSE EVENTS AND UNEXPECTED ADVERSE EVENTS – DEFINITIONS

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

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

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

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

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

11.5. SERIOUS ADVERSE EVENTS – REPORTING

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

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

Premier Research Global Pharmacovigilance
PVDS-NA@premier-research.com

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.

Sites are to follow their IRB/EC requirements for reporting SAEs/AEs.

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

In the event of any SAE (other than death), the subject will be instructed to contact the study physician (Principal Investigator or designee) using the phone number provided in the

Informed Consent Form. All subjects experiencing an SAE will be seen by a Principal Investigator or designee as soon as feasible following the report of an SAE.

12. STATISTICAL CONSIDERATIONS

12.1. ANALYSIS POPULATION

The Safety Analysis Set includes all subjects who receive study treatment.

12.2. SAFETY ANALYSIS

Adverse events reported on CRFs 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 Study Day 1 values.

12.3. HBA1C ANALYSIS

HbA1c levels will be collected and measured repeatedly from all subjects for whom a Day 1 HbA1c has been collected (including re-entry subjects), and these data will be analyzed by a linear mixed model for repeated measurements. Two subject cohorts will be analyzed separately: those randomized to placebo in the PTI-125-06 or PTI-125-07 phase 3 studies, and those randomized to simufilam in those studies. The analytical model will be fully described in the statistical analysis plan.

12.4. PLASMA BIOMARKER ANALYSIS

Plasma assays may include P-tau217, glial fibrillary acidic protein, neurofilament light, and other biomarkers. All plasma biomarker data measured repeatedly will be analyzed by linear mixed models for repeated measurements. Subject cohorts of interest for separate analyses include subjects who participated in one of the plasma biomarker sub-studies of the PTI-125-06 or PTI-125-07 phase 3 studies; subjects randomized to placebo and subjects randomized to simufilam in the aforementioned studies. Within-subject change from baseline analyses may also be conducted. The analytical model and all other analyses will be fully described in the statistical analysis plan.

12.5. CLINICAL DEMENTIA RATING

CDR sum of boxes and/or global score assessments measured repeatedly will be analyzed using a linear mixed model for repeated measurements. Two subject cohorts will be analyzed separately: those randomized to placebo in the PTI-125-06 or PTI-125-07 phase 3 studies, and those randomized to simufilam in those studies. Within-subject change from baseline may also be conducted. The analytical model and all other analyses will be fully described in the statistical analysis plan.

12.6. INTERIM ANALYSIS

Interim analysis of plasma biomarker and cognitive data may occur at the discretion of the sponsor.

13. STUDY TERMINATION

The study will be terminated following approval by the FDA of simufilam for the treatment of Alzheimer's disease or at any time at the discretion of the Sponsor.

14. DATA COLLECTION, RETENTION AND MONITORING

14.1. CASE REPORT FORMS

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

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

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

14.2. AVAILABILITY AND RETENTION OF INVESTIGATIONAL RECORDS

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

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

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

14.3. SUBJECT CONFIDENTIALITY

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

14.4. LIABILITY

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

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

14.5. 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.

14.5.1. Institutional Review Board / Ethics Committee

The protocol, ICF, clinical sites and Investigators must be approved by an IRB/EC before the study is initiated. The IRB/EC must comply with U.S. CFR 21 Part 56 or local regulatory and ICH requirements if outside the United States.

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

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

The Investigator is responsible for:

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

14.6. INFORMED CONSENT FORM

The Sponsor will submit the Informed Consent Form (ICF) to the central IRB for approval. An IRB-approved copy of the ICF will be forwarded to the Investigator and/or site staff.

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

15. INVESTIGATOR RESPONSIBILITIES

The Investigator agrees to:

- Conduct the study in accordance with the protocol, except to protect the safety, rights, or welfare of subjects.
- Personally conduct or supervise the study.
- Ensure that requirements for obtaining informed consent and IRB review and approval comply with ICH, CFR 21 Parts 50 and 56, or local regulatory and ICH requirements if outside of the United States.
- 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 study drug.
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate records in accordance with ICH, 21 CFR Part 312.62, and local laws and have records available for inspection by the Sponsor, FDA, or other authorized agency.

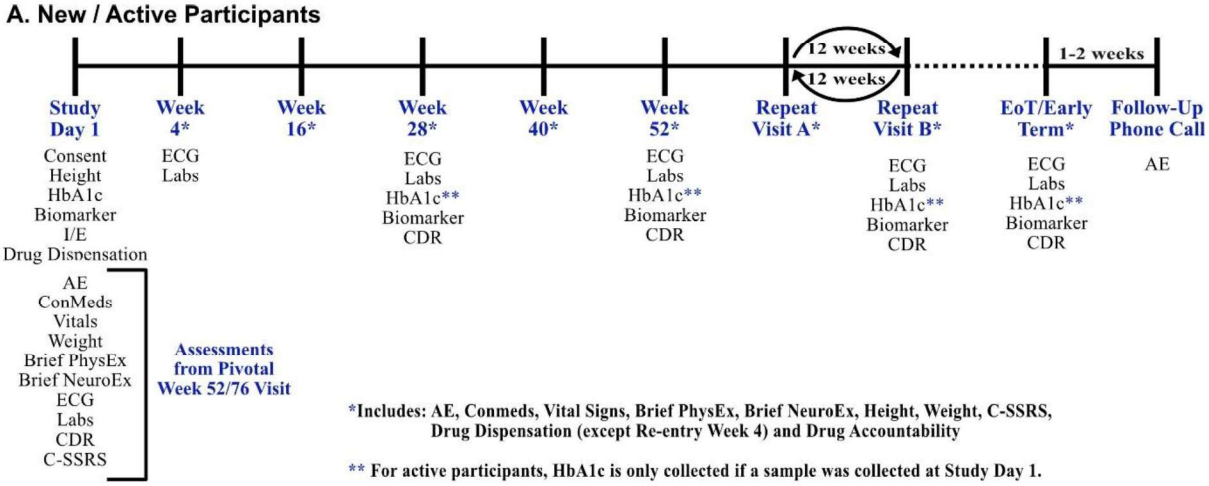
- Promptly report to the IRB and the Sponsor all changes in research activity and unanticipated problems involving risks to subjects or others (including amendments and expedited safety reports).
- Comply with all other requirements regarding obligations of Clinical Investigators and all other pertinent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

16. REFERENCES

1. Wang, H. Y., Cecon, E., Dam, J., Pei, Z., Jockers, R., & Burns, L. H. (2023). Simufilam Reverses Aberrant Receptor Interactions of Filamin A in Alzheimer's Disease. *International journal of molecular sciences*, *24*(18), 13927. https://doi.org/10.3390/ijms241813927.
2. Morris J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, *43*(11), 2412–2414. https://doi.org/10.1212/wnl.43.11.2412-a
3. O'Bryant, S. E., Lacritz, L. H., Hall, J., Waring, S. C., Chan, W., Khodr, Z. G., Massman, P. J., Hobson, V., & Cullum, C. M. (2010). Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. *Archives of neurology*, *67*(6), 746–749. https://doi.org/10.1001/archneurol.2010.115
4. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. American Journal of Psychiatry 2011;168(12):1266-77.

17. APPENDIX A – STUDY DESIGN SCHEMATIC

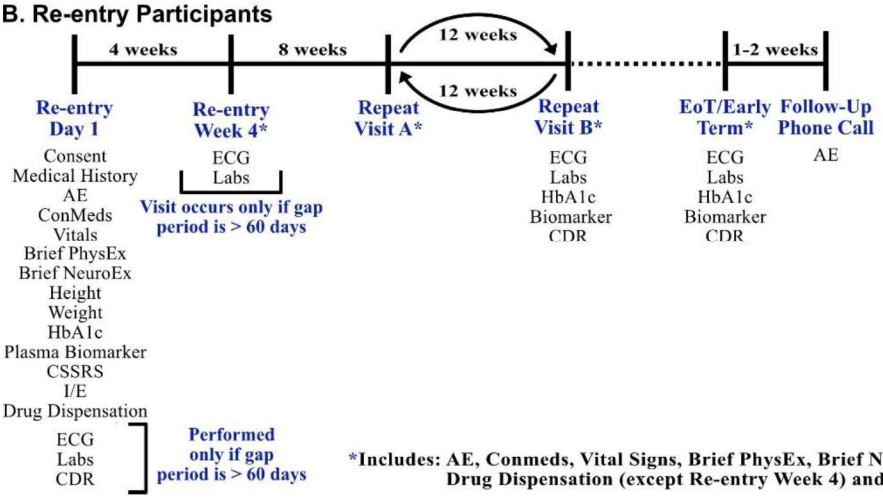
A. New / Active Participants



*Includes: AE, Conmeds, Vital Signs, Brief PhysEx, Brief NeuroEx, Height, Weight, C-SSRS, Drug Dispensation (except Re-entry Week 4) and Drug Accountability

** For active participants, HbA1c is only collected if a sample was collected at Study Day 1.

B. Re-entry Participants



*Includes: AE, Conmeds, Vital Signs, Brief PhysEx, Brief NeuroEx, Height, Weight, C-SSRS, Drug Dispensation (except Re-entry Week 4) and Drug Accountability.

18. APPENDIX B – SCHEDULE OF ACTIVITIES FOR NEW/ACTIVE PARTICIPANTS

Procedures	Study Day 1	Wk 4	Wk 16	Wk 28	Wk 40	Wk 52	Repeat Visit A[5]	Repeat Visit B[6]	EoT/Early Term	Follow-up Phone Call[8]
Informed Consent	X									
I/E Criteria	X									
Adverse Events	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	
Brief Physical Examination	X	X	X	X	X	X	X	X	X	
Brief Neurologic Examination	X	X	X	X	X	X	X	X	X	
Height	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	
Resting ECG	X	X		X		X		X	X	
Biochemistry, Hematology, Urinalysis	X	X		X		X		X	X	
HbA1c	X			X[4]		X[4]		X[4]	X[4]	
Plasma Biomarkers[1]	X			X		X		X	X	
CDR	X			X		X		X	X[7]	
C-SSRS[2]	X	X	X	X	X	X	X	X	X	
Study Drug Dispensation	X[3]	X	X	X	X	X	X	X		
Study Drug Accountability		X	X	X	X	X	X	X	X	
End of Study Follow-up Phone Call										X

[1]Plasma Biomarker collection will begin upon receipt of required supplies.

[2]On Study Day 1, as well as all remaining visits, the 'C-SSRS Since Last Visit' version will be administered.

[3]The first dose of study drug is administered at the clinic to all subjects on Study Day 1 at least four hours after any prior dose and at least one hour before departure.

[4]HbA1c should only be collected in subjects with a Study Day 1 HbA1c.

[5]Repeat Visit A occurs 12 weeks following the Week 52 visit and then reoccurs every 24 weeks thereafter.

[6]Repeat Visit B occurs 12 weeks following the first Repeat Visit A visit and then reoccurs every 24 weeks thereafter.

[7]CDR is only performed at the End of Treatment visit.

[8]Follow-up phone call occurs 1-2 weeks after End of Treatment/Early Termination.

19. APPENDIX C – SCHEDULE OF ACTIVITIES FOR RE-ENTRY PARTICIPANTS

Procedures	Re-entry Day 1	Re-entry Wk 4[5]	Repeat Visit A[6]	Repeat Visit B[7]	EoT / Early Term	Follow-up Phone Call[9]
Informed Consent	X					
Medical History	X					
I/E Criteria	X					
Adverse Events	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	
Vital Signs	X	X	X	X	X	
Brief Physical Exam	X	X	X	X	X	
Brief Neurologic Exam	X	X	X	X	X	
Height	X	X	X	X	X	
Weight	X	X	X	X	X	
Resting ECG	X[1]	X		X	X	
Biochemistry, Hematology, Urinalysis	X[1]	X		X	X	
HbA1c	X			X	X	
Plasma Biomarkers[2]	X			X	X	
CDR	X[1]			X	X[8]	
C-SSRS[3]	X	X	X	X	X	
Study Drug Dispensation	X[4]		X	X		
Study Drug Accountability		X	X	X	X	
End of Study Follow-up Phone Call						X

[1]Resting ECG, Biochemistry, Hematology, Urinalysis, and CDR to be performed only for Re-entry Day 1 subjects who completed the PTI-125-10 Week 52 visit >60 days prior to re-entry.

[2]Plasma Biomarker collection will begin upon receipt of required supplies.

[3]On Re-entry Day 1, as well as all remaining visits, the 'C-SSRS Since Last Visit' version will be administered.

[4]The first dose of study drug is administered at the clinic to all subjects at least one hour before departure.

[5]Re-entry Week 4 visit performed only for Re-entry subjects who completed PTI-125-10 Week 52 visit >60 days prior to re-entry.

[6]Repeat Visit A occurs 12 weeks following the Re-entry Day 1 visit and then reoccurs every 24 weeks thereafter.

[7]Repeat Visit B occurs 12 weeks following the first Repeat Visit A and then reoccurs every 24 weeks thereafter.

[8]CDR is only performed at the End of Treatment visit.

[9]Follow-up phone call to occur 1-2 weeks after End of Treatment/Early Termination.