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CLINICAL RESEARCH PROTOCOL
PROTOCOL PTI-125-09

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 Patients

Sponsor:	**Cassava Sciences, Inc.** 6801 N. Capital of Texas Hwy Building 1, Suite 300 Austin, TX 78731
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Protocol Date:	February 18, 2022
Amendment #1 Date:	December 22, 2022
Amendment #2 (Canada Only) Date:	March 22, 2023
Amendment #3 Date:	**September 18, 2024**

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

1. LIST OF ABBREVIATIONS

Updated:

~~AChEI acetylcholinesterase inhibitor~~
~~ADAS-Cog11 Alzheimer's Disease Assessment Scale cognitive subscale 11~~
~~ELISA enzyme-linked immunosorbent assay~~
~~IR insulin receptor~~
~~NMDAR N-methyl D-aspartate receptor~~
~~NPI neuropsychiatric inventory~~
~~PAL Paired Associate Learning~~
~~TLR4 toll-like receptor 4~~
~~YKL-40 chitinase-like protein 1, a secreted glycoprotein associated with inflammation and tissue remodeling~~

2.1 Mechanism of Action

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

Updated: A robust nonclinical ADME, safety pharmacology, and general and genetic toxicology program has been conducted with simufilam. In vitro metabolic profiling showed minimal metabolism across several species including humans. Simufilam was rapidly absorbed and eliminated in in vivo studies in rat and dog with nearly 100% oral bioavailability, a 2.67-h half-life in dog, dose-proportional PK and no accumulation. Simufilam does not inhibit or induce major CYP450 enzymes, nor is a substrate or inhibitor of major human drug transporters at clinically relevant concentrations. Safety pharmacology studies showed no adverse effects on

gross behavioral and physiological parameters in the Irwin test of CNS toxicity in rats, no adverse effects on respiratory rate, tidal volume or minute volume in the rat respiratory test, and no adverse effects on arterial blood pressure, heart rate and ECG parameters in the dog cardiovascular study. The in vitro hERG test for cardiotoxicity also indicated no adverse effect. A full battery of genotoxicity studies was conducted (in vitro bacterial Ames, in vitro chromosomal aberration, and in vivo rat micronucleus test) and were all negative. An in vitro specificity screen showed no significant activation or inhibition of a panel of 68 receptors, channels, and transporters.

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

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 (**Figure 1**).[4] $A\beta_{42}$, which is low in AD, was increased slightly but non-significantly. Reduced inflammatory cytokines and YKL-40 indicated reduced neuroinflammation. A reduced neurodegenerative drive was suggested by reductions in neurogranin, neurofilament light chain, and total tau. The robust reduction in phospho-tau (p-tau181) confirms the mechanism of action of simufilam.~~ Simufilam was safe and well tolerated in all subjects.

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

~~***2.3.3. Double-Blind Placebo-Controlled Clinical Trial in Mild-to-Moderate AD Patients***~~

A phase 2b randomized, placebo-controlled clinical study (PTI-125-02) of simufilam 50 or 100 mg tablets or placebo (1:1:1) enrolled 64 mild-to-moderate AD subjects with MMSE 16-26. ~~Both 50 and 100 mg doses significantly reduced plasma p-tau181, consistent with data seen with CSF biomarkers (**Figure 2**). These data suggest disease modification and replicate Phase 2a results in~~

~~a well-controlled study.~~ Similar to the phase 2a study, simufilam was safe and well tolerated and no subjects discontinued due to AEs.

~~**Figure 2 Phase 2b Mean Change from Baseline to Day 28 in plasma p-tau181 (±SD)**~~

~~The secondary endpoints in the Phase 2b trial were two cognitive measures using the Cambridge Neuropsychological Test Automated Battery. Subjects were assessed on the Paired Associates Learning (PAL) test, measuring episodic memory, and a test of spatial working memory. The primary outcome measures for each were total errors, with errors imputed for more difficult levels not reached in the PAL test. Simufilam produced encouraging mean improvements from baseline in spatial working memory and in a sensitivity analysis for episodic memory for both doses, suggesting cognitive enhancement (**Figure 3**). Subjects who showed no detectable simufilam in plasma or >25% noncompliance by pill counts were excluded from cognitive data (5 subjects). For the sensitivity analysis for episodic memory, the most and least impaired subjects were removed by baseline score. Cognitive enhancement by simufilam is supported by preclinical data showing improved function of α7nAChR, NMDAR and insulin receptors and improved synaptic plasticity in 3xTg AD mice and in postmortem human AD brain tissue. In both Phase 2 clinical trials, simufilam was well tolerated.~~

~~**Figure 3 Phase 2b Mean Reduction from Baseline in Total Errors in Cognition Tests**~~

~~*2.3.4. Ongoing 12-Month, Open-Label Safety Study of Simufilam followed by a 6-Month Randomized Withdrawal and 6 Additional Months Open-Label in Mild-to-Moderate Alzheimer's Disease Patients*~~

~~To assess longer-term clinical safety of simufilam, a 1-year, open-label clinical trial of simufilam 100 mg b.i.d. is ongoing in 220 mild-to-moderate AD subjects. The protocol was amended to add a 6-month double-blind period where patients will either continue taking simufilam or be switched to placebo. An additional 6 months of open-label simufilam follows this randomized period. All prior simufilam study participants were eligible, and new patients (MMSE 16-26) were also able to enroll.~~

~~The first 50 patients to complete 6, 9 and 12 months of treatment showed *mean improvements* on ADAS-Cog11 of 1.6, 3.0 and 3.2 points, respectively (**Figure 4**). This improvement from baseline contrasts with an expected decline of ~2.5 points at 6 months and 5.5 points over one year.[5] The improvement in this population at 6 months suggests cognitive enhancement and possibly also a slowing of decline. On the 10-item Neuropsychiatric Inventory (NPI-10), the percentage of subjects showing no symptoms (score of 0) increased from 34% at baseline to over 50% at 9 and 12 months. This scale measures AD-related neuropsychiatric symptoms such as irritability, delusions, and paranoia.~~

~~**Figure 4 ADAS-Cog11 Improvement from Baseline in First 50 Subjects to Complete 6, 9 and 12 Months**~~

~~Twenty-five (25) subjects provided CSF samples at baseline and 6 months. This longer-term assessment of biomarkers showed more profound improvements than seen after 28 days of treatment, all highly significant by paired *t* test ($p<0.0001$) (**Figure 5**).~~

~~**Figure 5 Percent Change from Baseline in CSF Biomarkers at 6 Months**~~

~~Safety data shows that simufilam continues to be safe and well tolerated. There were no serious adverse events reported that were related to study drug.~~

~~***2.3.5. Food Effect and Bioequivalence Study***~~

~~A four-way cross-over study was conducted in healthy volunteers, age 18-45, to determine the effect of food on the PK of simufilam. There was no significant difference between fasting, low-fat, or high-fat meals on AUClast, indicating no effect of food. The study also compared the Phase 2 oral tablet with the Phase 3 oral tablet and found no difference in AUClast, establishing bioequivalence between the formulations.~~

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 3 clinical studies:

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.

PTI-125-10 is phase 3, open-label extension study evaluating the safety and long-term treatment of simufilam in mild-to-moderate Alzheimer's disease subjects. Enrollment began 4Q2022 and is only available to subjects who have completed the PTI-125-06 and PTI-125-07 protocols. The study is designed to last until the United States Food and Drug administration approves

simufilam as a treatment for AD or until program termination.

3. STUDY OBJECTIVES

Updated: The objective of this study is to establish an open label extension following study PTI-125-04 or who already completed participation through Week 96 in PTI-125-09 to investigate the long-term safety of simufilam in subjects with mild-to-moderate AD .

4. SUMMARY OF STUDY DESIGN

Updated: This is an ~~96-week~~ extension study of open-label simufilam 100 mg b.i.d. for subjects who completed the Phase 2 study, PTI-125-04 or who already completed participation through Week 96 in PTI-125-09. This extension study will continue through FDA approval of simufilam or program termination (Appendix A). All subjects will provide consent to enroll into this study. Simufilam will be administered as coated oral tablets.

The last study visit, Month 24, from the PTI-125-04 study will be used for the Study Day 1 visit assessments in this extension study. Clinic visits will occur every 12 weeks ±10 days as outlined in ~~Appendix A – Schedule of Events.~~ Appendix B – Schedule of Events for Active Participants.

Subjects who already completed participation through Week 96 in PTI-125-09 will have the option to return to the study and resume participation. After the subject provides consent, the Investigator will confirm that the subject continues to satisfy both the inclusion and exclusion 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 according to Appendix C – Schedule of Events for Re-entry Participants.

For active subjects, a ~~complete~~ full physical examination (general appearance, chest/lungs, heart, abdomen, skin, musculoskeletal, Neurologic, Vascular, and Immunologic) will be performed at Study Day 1, Week 48 ~~visit~~, ~~and~~ Week 96 ~~visit,~~ and Repeat Visit B until study end. For re-entry subjects, a full physical examination will occur on Re-entry Day 1 and Repeat Visit B thereafter until study ends. All subjects will return to the clinic every 12 weeks for AE monitoring, vital sign measurements, height, weight, Columbia Suicide Severity Rating Scale (C-SSRS)[2], and drug dispensation and accountability. Some re-entry participants will require a Re-entry week 4 visit. A brief physical exam (general appearance, cardiovascular, pulmonary, and abdominal examination, as well as an examination of any other system in response to subject-reported symptoms) will occur at all visits that do not have a full physical exam.

Blood draws for clinical laboratory testing, urine collection for urinalysis, and ECGs will be performed at Study Day 1 ~~, and~~ Week~~s~~ 24, 48, 72, and 96, Re-entry Day 1 (if applicable), Re-Entry Week 4 (if applicable), and Repeat Visit B until study end.

Safety will be evaluated by adverse event monitoring, vital signs, clinical labs, and the ~~Columbia Suicide Severity Rating Scale (~~C-SSRS~~)~~.

5.2 Inclusion Criteria

Updated: 1. Must have completed the PTI-125-04 study or Week 96 in the PTI-125-09 study.

5.3 Exclusion Criteria
Updated: Anything that in the opinion of the Investigator would preclude participation in this ~~96 week~~ extension study. For anyone resuming study participation, any significant medical event or hospitalization during the gap period must be discussed with the medical monitor.

7. STUDY PROCEDURES
Updated: ~~Appendix A – Schedule of Events~~ Appendix B – Schedule of Events for Active Participants and Appendix C – Schedule of Events for Re-entry Participants presents the schedule of activities.

7.2. Evaluations By Visit
Updated:

7.2.1. Study Day 1 (Dosing initiation)

- Review of concomitant medications
- Full ~~P~~physical examination including measurement of vital signs (blood pressure, temperature, pulse, and respiratory rate), height, weight

7.2.2. Follow-up Visits on Weeks 12, 36, 60, and 84

Subjects will return to clinic and the following assessments will be conducted:

- Height
- Weight
- Brief physical exam ~~Listen to heart and lungs~~

7.2.3. Follow-up Visits on Weeks 24, ~~48,~~ and 72

Subjects will return to clinic and the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Height
- Weight
- Brief physical exam ~~Listen to heart and lungs~~
- ~~Full physical exam (**Week 48 only**)~~
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

7.2.4. Follow-up Visits on Weeks 48 and 96

Subjects will return to clinic and the following assessments will be conducted:

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

- Height
- Weight
- Full physical exam
- Adverse event monitoring
- Use of concomitant medications
- Clinical laboratory tests (blood and urine)
- ECG
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

7.2.5 Repeat Visit A

Repeat Visit A occurs 12 weeks following the Week 96 visit for active participants or 12 weeks following the Re-entry Day 1 visit for re-entry participants, and then reoccurs every 24 weeks thereafter.

Subjects will return to clinic and the following assessments will be conducted:

- Height
- Weight
- Brief physical exam
- Measure vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Adverse event monitoring
- Use of concomitant medications
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

All repeat visits can be ±10 (ten) days for flexibility.

7.2.6 Repeat Visit B

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

Subjects will return to clinic and the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Height
- Weight
- Full physical exam
- Adverse event monitoring
- Use of concomitant medications
- Clinical laboratory tests (blood and urine)
- ECG
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

All repeat visits can be ±10 (ten) days for flexibility.

7.2.7. ~~Week 96~~ End of ~~Treatment~~ Study / Early Termination (ET) Visit

Subjects will return to clinic and the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Height
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

7.2.8 Re-entry for Subjects Who Previously Completed (Re-entry Day 1)

Subjects who completed the final visit on the PTI-125-09 study on Amendment 1 or Amendment 2 will be eligible to re-enter this open-label extension study if the subject does not meet exclusion criterion.

Subjects will come to the clinic for a Re-entry Day 1 visit and the following will be conducted:

- Informed Consent
- Medical History- focused on any new conditions that occurred during the gap period between study completion and study re-entry

- Vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Height
- Weight
- Full physical exam
- Adverse event monitoring
- Use of concomitant medications
- Clinical laboratory tests (blood and urine)
- ECG
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Review of Inclusion and Exclusion criteria following all Re-entry Day 1 assessments and prior to dosing.

Subjects will be administered one (1) tablet of study drug at the clinic. Subjects will be discharged with their supply of study drug until the next visit. They will be instructed to take study drug twice daily, with or without food. A dose can be up to 4 hours late, but if a dose is missed, the next dose should NOT be doubled.

Follow-up visits will continue as indicated in Appendix C – Schedule of Events for Re-entry Participants. For all follow-up visits, subjects will be instructed to bring their study drug bottle to the clinic and a new bottle of study drug will be dispensed (except at the Re-entry Week 4 visit if required).

7.2.9 Re-entry Week 4 (Only for Re-entry Day 1 Subjects Who Complete Re-entry Day 1 Visit >60 Days After Completing PTI-125-09))

Subjects who completed Re-entry Day 1 Visit >60 days after completing their original study participation of PTI-125-09 will have a visit performed 4 weeks after Re-entry Day 1.

Subjects will come to the clinic for a Re-entry Week 4 visit and the following will be conducted:

- Vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Height
- Weight
- Brief physical exam
- Adverse event monitoring

- Use of concomitant medications
- Clinical laboratory tests (blood and urine)
- ECG
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.

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.

Follow-up visits will continue as indicated in Appendix C – Schedule of Events for Re-entry Participants, starting with Week 12. For all follow-up visits, subjects will be instructed to bring their study drug bottle to the clinic and a new bottle of study drug will be dispensed.

Re-entry Week 4 visit can be ±10 (ten) days for flexibility.

7.3 Laboratory Assessments
Updated: The following clinical laboratory tests will be performed at Study Day 1, ~~and~~ at Week~~s~~ 24,~~-~~48, 72, and 96, Re-entry Day 1 (if applicable), Re-entry Week 4 (if applicable), and Repeat Visit B until study end:

8. Early Discontinuation
Updated:

- Vital signs (blood pressure, temperature, pulse, and respiratory rate), height, weight, full physical exam, clinical laboratory tests, ECG, use of concomitant medications, and adverse events should be obtained at discharge prior to release.

9.5 Serious Adverse Events Reporting
Updated: All SAEs must be reported immediately **(within 24 hours of learning of the event)** ~~by telephone or notification via email through the~~ via entry into the EDC system with at least the event term, start date, and IP relationship. In the event EDC entry is unavailable, notification must occur via email or phone to the contact below ~~to~~:

James W. Kupiec, MD
Cassava Sciences, Inc.
Email: SAEReview@cassavasciences.com
Phone: 860-514-6900

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.

If a partial SAE report was initially provided then a ~~A~~ complete SAE report ~~form~~ must be entered into the EDC ~~sent~~ within five (5) working days ~~to the medical monitor~~. The Investigator is responsible for reporting SAEs to the IRB according to IRB guidelines. The Sponsor will report SAEs to ~~the IRB and~~ FDA as required.

11. STUDY TERMINATION

Updated: The study will be terminated following ~~completion of the study~~ FDA approval of simufilam or program termination or at any time at the discretion of the Sponsor.

14. REFERENCES

Updated:

1. ~~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.~~
2. ~~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.~~
3. ~~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.~~
4. ~~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.~~
5. ~~Ito K, Adieh S, Corrigan B, French J, Fullerton T, Tensfeldt T, Alzheimer's disease Working Group. Disease progression meta-analysis model in Alzheimer's Disease. 2010;6:39-53.~~
6. ~~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.~~

1. Wang, H. Y., Cecon, E., Dam, J., Pei, Z., Jockers, R., & Burns, L. H. (2023). Simufilam Reverses Abcrrant Rcccptor Intcractions of Filamin A in Alzhcimcr's Discasc. *International journal of molecular sciences*, *24*(18), 13927. https://doi.org/10.3390/ijms241813927.
2. 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:

15: Appendix A: Study Design Schematic

Changed:

15: Appendix A: Schedule of Events to 16: Appendix B: Schedule of Events for Active Participants

Added:

17: Appendix C: Schedule of Events for Re-entry Participants

The following revision is only applicable to U.S. sites.

4. SUMMARY OF STUDY DESIGN

Updated:

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.

5.2 Inclusion Criteria

Updated: 2. 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

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

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Approvals:

Signed by:
Michael Marsman, PharmD
Signer Name: Michael Marsman, PharmD
Signing Reason: I approve this document
Signing Time: 18-Sep-2024 | 16:50 CDT
6252303FF961490FACFF567B84CF70BC

18-Sep-2024 | 16:50 CDT

Michael Marsman, PharmD
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Cassava Sciences, Inc.

Date

Signed by:
James W. Kupiec, MD
Signer Name: James W. Kupiec, MD
Signing Reason: I approve this document
Signing Time: 18-Sep-2024 | 17:06 CDT
9D60F9221DE944859AD2EE06ADD9083E

18-Sep-2024 | 17:11 CDT

James W. Kupiec, MD
Chief Medical Officer
Cassava Sciences, Inc.

Date

Signed by:
Ben J. Murray
Signer Name: Ben J. Murray
Signing Reason: I approve this document
Signing Time: 18-Sep-2024 | 16:30 CDT
F41B91D63A97466DB912EC70EC65745A

18-Sep-2024 | 16:31 CDT

Ben J. Murray, MS
Sr. Associate Director,
Clinical Project Management
Cassava Sciences, Inc.

Date

Cassava Sciences, Inc.

CLINICAL RESEARCH PROTOCOL

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 Patients

Signature of Agreement for Protocol PTI-125-09

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

_____ _____

Principal Investigator Signature Date

_____

Print Principal Investigator Name and Title

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

α7nAChR	α7 nicotinic acetylcholine receptor
$A\beta_{42}$	amyloid $beta_{1-42}$
AD	Alzheimer's disease
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the curve
b.i.d.	twice a day
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CNS	central nervous system
CRO	contract research organization
CSF	cerebrospinal fluid
CSI	Cassava Sciences, Inc.
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FLNA	filamin A
GCP	good clinical practice
GGT	gamma glutamyl transpeptidase
hERG	human ether-a-go-go-related gene
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
LDH	lactose dehydrogenase
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NOAEL	no observable adverse effect level
NOEL	no observable effect level
PK	pharmacokinetics
PTI-125	small molecule drug candidate to treat AD
RBC	red blood cell
SAE	serious adverse event
SOP	standard operating procedure
ULN	upper limit of normal
WBC	white blood cell

2. INTRODUCTION

2.1. MECHANISM OF ACTION

Cassava Sciences, Inc. (CSI) 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 amyloid beta$_{1-42}$ (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} persistently 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. SAFETY PHARMACOLOGY AND TOXICOLOGY

A robust nonclinical ADME, safety pharmacology, and general and genetic toxicology program has been conducted with simufilam. In vitro metabolic profiling showed minimal metabolism across several species including humans. Simufilam was rapidly absorbed and eliminated in in vivo studies in rat and dog with nearly 100% oral bioavailability, a 2.67-h half-life in dog, dose-proportional PK and no accumulation. Simufilam does not inhibit or induce major CYP450 enzymes, nor is a substrate or inhibitor of major human drug transporters at clinically relevant concentrations. Safety pharmacology studies showed no adverse effects on gross behavioral and physiological parameters in the Irwin test of CNS toxicity in rats, no adverse effects on respiratory rate, tidal volume or minute volume in the rat respiratory test, and no adverse effects on arterial blood pressure, heart rate and ECG parameters in the dog cardiovascular study. The in vitro hERG test for cardiotoxicity also indicated no adverse effect. A full battery of genotoxicity studies was conducted (in vitro bacterial Ames, in vitro chromosomal aberration, and in vivo rat micronucleus test) and were all negative. An in vitro specificity screen showed no significant activation or inhibition of a panel of 68 receptors, channels, and transporters.

Simufilam was tested in single dose and repeat dose oral toxicity studies of up to 6 months in rats and 9 months in dogs. A 6-month repeat dose oral toxicity study in rats (PTI-125-NC-049) used the same doses as a 28-day study (50, 500 and 1000 mg/kg/day), which found 500 mg/kg/day to be the no-observable-adverse-effect-level (NOAEL). In the 6-month study, the toxicological response was characterized by decreased body weights and adverse structural and functional alterations in the liver of 500 and 1000 mg/kg/day animals, including increased hepatic weight, hepatocellular hypertrophy and vacuolation, single/multiple basophilic/ eosinophilic/clear cell focus, hepatocellular degeneration, pigmentation, and oval cell hyperplasia. The presence of bile pigment was consistent with

cholestasis. These findings correlated with changes to the clinical chemistry profile, including increased ALP and total/direct bilirubin. Over the 1-month recovery period, there was complete recovery of the hepatocellular degeneration and partial recovery of hepatocellular hypertrophy; other microscopic findings in the liver remained. The NOAEL in this 6-month study was 50 mg/kg/day (equivalent to 300 mg/m^2), corresponding to a safety margin of 6- and 1.6-fold based on C_{max} and AUC over the 100 mg b.i.d. dose in human subjects. A second 6-month repeat dose oral toxicity study in rats determined the 6-month NOAEL in the rat to be < 125 mg/kg/day, based on hepatocellular vacuolation in both sexes and hepatocellular hypertrophy in females at 125 and 250 mg/kg. We are evaluating whether these liver effects are rat specific.

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

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

2.3. CLINICAL STUDIES

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

In a 28-day phase 2a study (PTI-125-03), 13 subjects with mild-to-moderate AD received simufilam 100 mg b.i.d. as oral tablets. Subjects had Mini-Mental State Exam (MMSE) scores ≥ 16 and ≤ 24 and were age 50-85 with a CSF total tau/Aβ_{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 16-26. 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 3 clinical studies:

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.

PTI-125-10 is phase 3, open-label extension study evaluating the safety and long-term treatment of simufilam in mild-to-moderate Alzheimer's disease subjects. Enrollment began 4Q2022 and is only available to subjects who have completed the PTI-125-06 and PTI-125-07 protocols. The study is designed to last until the United States Food and Drug administration approves simufilam as a treatment for AD or until program termination.

3. STUDY OBJECTIVES

The objective of this study is to establish an open label extension following study PTI-125-04 or who already completed participation through Week 96 in PTI-125-09 to investigate the long-term safety of simufilam in subjects with mild-to-moderate AD.

4. SUMMARY OF STUDY DESIGN

This is an extension study of open-label simufilam 100 mg b.i.d. for subjects who completed the Phase 2 study, PTI-125-04 or who already completed participation through Week 96 in PTI-125-09. This extension study will continue through FDA approval of simufilam or program termination (Appendix A). All subjects will provide consent to enroll into this study. Simufilam will be administered as coated oral tablets.

The last study visit, Month 24, from the PTI-125-04 study will be used for the Study Day 1 visit assessments in this extension study. Clinic visits will occur every 12 weeks ±10 days as outlined in Appendix B – Schedule of Events for Active Participants.

Subjects who already completed participation through Week 96 in PTI-125-09 will have the option to return to the study and resume participation. After the subject provides consent, the Investigator will confirm that the subject continues to satisfy both the inclusion and exclusion 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 according to Appendix C – Schedule of Events for Re-entry Participants.

For active subjects, a full physical examination (general appearance, chest/lungs, heart, abdomen, skin, musculoskeletal, Neurologic, Vascular, and Immunologic) will be performed at Study Day 1, Week 48, Week 96, and Repeat Visit B until study end. For re-entry subjects, a full physical examination will occur on Re-entry Day 1 and Repeat Visit B thereafter until study ends. All subjects will return to the clinic every 12 weeks for AE monitoring, vital sign measurements, height, weight, Columbia Suicide Severity Rating Scale (C-SSRS)[2], and drug dispensation and accountability. Some re-entry participants will require a Re-entry Week 4 visit. A brief physical exam (general appearance, cardiovascular, pulmonary, and abdominal examination, as well as an examination of any other system in response to subject-reported symptoms) will occur at all visits that do not have a full physical exam.

Blood draws for clinical laboratory testing, urine collection for urinalysis, and ECGs will be performed at Study Day 1,Weeks 24, 48, and 96, Re-entry Day 1 (if applicable), Re-Entry Week 4 (if applicable), and Repeat Visit B until study end.

Safety will be evaluated by adverse event monitoring, vital signs, clinical labs, and the C-SSRS.

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 180 subjects will be enrolled in the study (male and female).

5.2. INCLUSION CRITERIA

All subjects must comply with the following Inclusion Criteria:

1. Must have completed the PTI-125-04 study or Week 96 in the PTI-125-09 study.

2. 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.

5.3. EXCLUSION CRITERIA

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

1. Anything that in the opinion of the Investigator would preclude participation in this extension study. For anyone resuming study participation, any significant medical event or hospitalization during the gap period must be discussed with the medical monitor.

6. STUDY DRUG

6.1. STUDY DRUG PHYSICAL DESCRIPTION AND PREPARATION

Investigational simufilam will be supplied by CSI as coated tablets in 188-count bottles that provide 12 weeks of b.i.d. medication. Up to 10 days of extra medication is included in each bottle.

Each used bottle of medication is to be returned to the clinic regardless of whether medication remains.

6.1.1. Storage

Store medication at room temperature 20º-25ºC (68º-77ºF), protected from moisture.

6.1.2. Drug Accountability

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

6.2. ADMINISTRATION AND DOSING REGIMEN

Subjects will receive 100 mg simufilam b.i.d. during the study. Simufilam tablets 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 – Schedule of Events for Active Participants and Appendix C – Schedule of Events for Re-entry Participants presents the schedule of activities.

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

7.1. STOPPING CRITERIA

Liver chemistry threshold stopping criteria have been designed to 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.

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

7.2. EVALUATIONS BY VISIT

7.2.1. Study Day 1 (Dosing initiation)

Subjects who complete PTI-125-04 will be eligible to consent to this open-label extension. The Study Day 1 visit will occur in conjunction with the Month 24 visit of PTI-125-04.

Subjects will come to the clinic and, in addition to the Month 24 Visit activities for PTI-125-04, the following will be conducted:

- Informed Consent

The following end of study procedures required at the Month 24 Visit for the completion of study PTI-125-04 will serve as baseline information for this open-label extension study:

- Review of concomitant medications
- Full physical examination including measurement of vital signs (blood pressure, temperature, pulse, and respiratory rate), height, weight
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Blood and urine sample collection for clinical laboratory tests
- ECG
- Adverse event monitoring

Subjects will be administered one (1) tablet of study drug at the clinic. Subjects will be discharged with their supply of study drug until the next visit. They will be instructed

to take study drug twice daily, with or without food. 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 and a new bottle of study drug will be dispensed.

All follow-up visits can be ±10 (ten) days for flexibility.

7.2.2. Follow-up Visits on Weeks 12, 36, 60, and 84

Subjects will return to clinic and the following assessments will be conducted:

- Height
- Weight
- Brief physical exam
- Measure vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Adverse event monitoring
- Use of concomitant medications
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

7.2.3. Follow-up Visits on Weeks 24 and 72

Subjects will return to clinic and the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Height
- Weight
- Brief physical exam
- Adverse event monitoring
- Use of concomitant medications
- Clinical laboratory tests (blood and urine)
- ECG
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for

suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.

- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

7.2.4. Follow-up Visits on Weeks 48 and 96

Subjects will return to clinic and the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Height
- Weight
- Full physical exam
- Adverse event monitoring
- Use of concomitant medications
- Clinical laboratory tests (blood and urine)
- ECG
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

7.2.5. Repeat Visit A

Repeat Visit A occurs 12 weeks following the Week 96 visit for active participants or 12 weeks following the Re-entry Day 1 visit for re-entry participants, and then reoccurs every 24 weeks thereafter.

Subjects will return to clinic and the following assessments will be conducted:

- Height
- Weight
- Brief physical exam
- Measure vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Adverse event monitoring
- Use of concomitant medications

- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

All repeat visits can be ±10 (ten) days for flexibility.

7.2.6. Repeat Visit B

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

Subjects will return to clinic and the following assessments will be conducted:

- Vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Height
- Weight
- Full physical exam
- Adverse event monitoring
- Use of concomitant medications
- Clinical laboratory tests (blood and urine)
- ECG
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

All repeat visits can be ±10 (ten) days for flexibility.

7.2.7. End of Study / Early Termination (ET) Visit

Subjects will return to clinic and the following assessments will be conducted:

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

- Full physical exam
- Adverse event monitoring
- Use of concomitant medications
- Clinical laboratory tests (blood and urine)
- ECG
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, refer for appropriate care.
- Receive and count remaining tablets in each returned bottle of investigational product to assess adherence to BID dosing.

7.2.8. Re-entry Day 1(Re-entry for Subjects Who Previously Completed)

Subjects who completed the final visit on the PTI-125-09 study on Amendment 1 or Amendment 2 will be eligible to re-enter this open-label extension study if the subject does not meet exclusion criterion.

Subjects will come to the clinic for a Re-entry Day 1 visit and the following will be conducted:

- Informed Consent
- Medical History- focused on any new conditions that occurred during the gap period between study completion and study re-entry
- Vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Height
- Weight
- Full physical exam
- Adverse event monitoring
- Use of concomitant medications
- Clinical laboratory tests (blood and urine)
- ECG
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.
- Review of Inclusion and Exclusion criteria following all Re-entry Day 1

assessments and prior to dosing.

Subjects will be administered one (1) tablet of study drug at the clinic. Subjects will be discharged with their supply of study drug until the next visit. They will be instructed to take study drug twice daily, with or without food. A dose can be up to 4 hours late, but if a dose is missed, the next dose should NOT be doubled.

Follow-up visits will continue as indicated in Appendix C- Schedule of Events for Re-entry Participants. For all follow-up visits, subjects will be instructed to bring their study drug bottle to the clinic and a new bottle of study drug will be dispensed (except at the Re-entry Week 4 visit if required).

7.2.9. Re-entry Week 4 (Only for Re-entry Day 1 Subjects Who Complete Re-entry Day 1 Visit >60 Days After Completing PTI-125-09)

Subjects who completed Re-entry Day 1 Visit >60 days after completing their original study participation of PTI-125-09 will have a visit performed 4 weeks after Re-entry Day 1.

Subjects will come to the clinic for a Re-entry Week 4 visit and the following will be conducted:

- Vital signs (blood pressure, temperature, pulse, and respiratory rate)
- Height
- Weight
- Brief physical exam
- Adverse event monitoring
- Use of concomitant medications
- Clinical laboratory tests (blood and urine)
- ECG
- C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, discontinue study drug and refer for appropriate care.

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.

Follow-up visits will continue as indicated in Appendix C – Schedule of Events for Re-entry Participants, starting with Week 12. For all follow-up visits, subjects will be

instructed to bring their study drug bottle to the clinic and a new bottle of study drug will be dispensed.

Re-entry Week 4 visit can be ±10 (ten) days for flexibility.

7.3. LABORATORY ASSESSMENTS

7.3.1. Clinical Laboratory Tests

The following clinical laboratory tests will be performed at Study Day 1,Weeks 24, 48, and 96, Re-entry Day 1 (if applicable), Re-entry Week 4 (if applicable), and Repeat Visit B until study end:

- Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count.
- Serum Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphate, blood urea nitrogen (BUN), total bilirubin, creatinine, cholesterol, triglycerides, albumin, globulin, total protein, uric acid, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), lactose dehydrogenase (LDH).
- Urinalysis: color, specific gravity, pH, protein, sugar, ketones, occult blood, creatinine clearance calculation by Cockcroft-Gault equation (without requiring a 24-h urine collection).

8. EARLY DISCONTINUATION

Subjects, Investigators, and the Sponsor may choose to have a subject discontinue study drug or study participation at any time, for any reason, and without prejudice.

The following must be completed and documented in the source documents and the electronic case report forms (eCRFs) for all subjects who discontinue the study early:

- The reason for early study discontinuation.
- Vital signs (blood pressure, temperature, pulse, and respiratory rate), height, weight, full physical exam, clinical laboratory tests, ECG, use of concomitant medications, and adverse events should be obtained at discharge prior to release.
- Administer the C-SSRS – Since Last Visit version. If the C-SSRS indicates imminent risk for suicidality, defined as the subject positively endorsing questions 4 or 5 of the suicidal ideation section or any suicidal behavior questions, immediately contact the sponsor.

9. ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

9.1. ADVERSE EVENTS - DEFINITION

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

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

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

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

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

9.2. ADVERSE EVENTS - SEVERITY RATING

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

- Mild – the AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.

- Moderate – the AE produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment.
- Severe – the AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

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

9.3. 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.

9.4. SERIOUS ADVERSE EVENTS AND UNEXPECTED ADVERSE EVENTS - DEFINITIONS

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

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

In addition, medical and scientific judgment should be exercised in deciding whether other situations should be considered an SAE (i.e., important medical events that may not be immediately life-threatening or result in death but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes

listed in the definition above). Examples of such medical events include (but are not limited to): allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

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

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

9.5. SERIOUS ADVERSE EVENTS REPORTING

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

All SAEs must be reported immediately **(within 24 hours of learning of the event)** via entry into the EDC system with at least the event term, start date, and IP relationship. In the event EDC entry is unavailable, notification must occur via email or phone to the contact below:

James W. Kupiec, MD
Cassava Sciences, Inc.
Email: SAEReview@cassavasciences.com
Phone: 860-514-6900

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.

If a partial SAE report was initially provided then a completed SAE report must be entered into the EDC within five (5) working days. The Investigator is responsible for reporting SAEs to the IRB according to IRB guidelines. The Sponsor will report SAEs to FDA as required.

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

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

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

10. STATISTICAL CONSIDERATIONS

10.1. ANALYSIS POPULATIONS

All subjects who receive study medication will be included in safety analyses.

10.2. SAFETY ANALYSIS

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

10.3. SAMPLE SIZE

Up to 180 subjects may be enrolled in this study. Eligible subjects include those who completed PTI-125-04.

11. STUDY TERMINATION

The study will be terminated following FDA approval of simufilam or program termination or at any time at the discretion of the Sponsor.

12. DATA COLLECTION, RETENTION AND MONITORING

12.1. CASE REPORT FORMS

Electronic case report forms (eCRFs) will be used for each subject. The 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 eCRFs provided by CSI. In case of error, the correction will be noted, initialed, and dated.

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

12.2. AVAILABILITY AND RETENTION OF INVESTIGATIONAL RECORDS

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

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

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

12.3. SUBJECT CONFIDENTIALITY

All reports and subject samples will be identified only by the assigned 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.

12.4. LIABILITY

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

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

12.5. ETHICAL AND LEGAL ISSUES

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

12.5.1. Institutional Review Board

The protocol and Informed Consent Form must be approved by an IRB before the study is initiated. The IRB must comply with U.S. CFR 21 Part 56 and local laws.

Documentation of IRB approval must be provided to the Sponsor. Investigators are responsible for the following:

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

12.6. INFORMED CONSENT FORM

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

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

13. INVESTIGATOR RESPONSIBILITIES

The Investigator agrees to:

- Conduct the study in accordance with the protocol, except to protect the safety,

rights, or welfare of subjects.

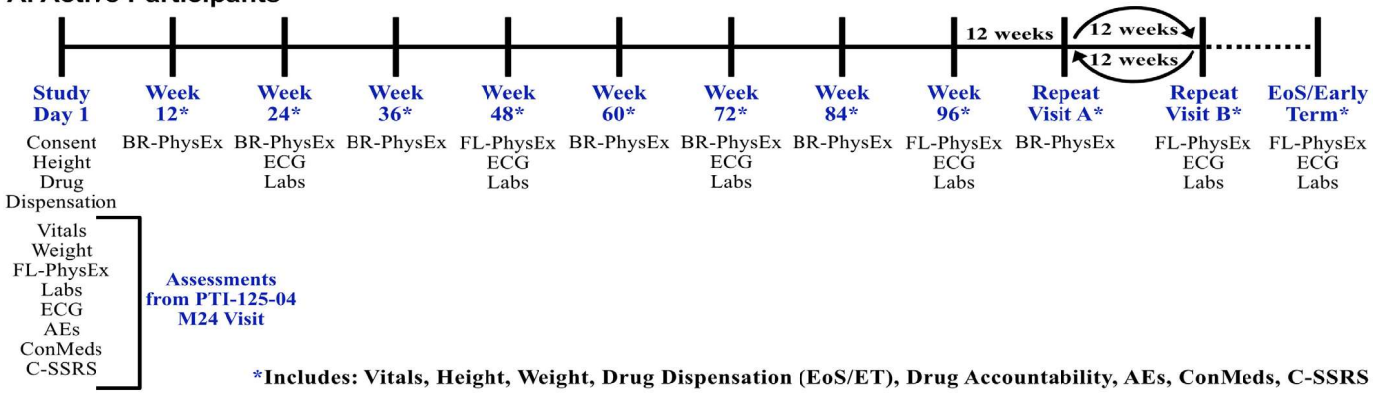
- Personally conduct or supervise the study.
- Ensure that requirements for obtaining informed consent and IRB review and approval comply with ICH, CFR 21 Parts 50 and 56, and local laws.
- Report to the Sponsor any AEs that occur during the study in accordance with ICH, CFR 21 Part 312.64, and local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

14. 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. 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.

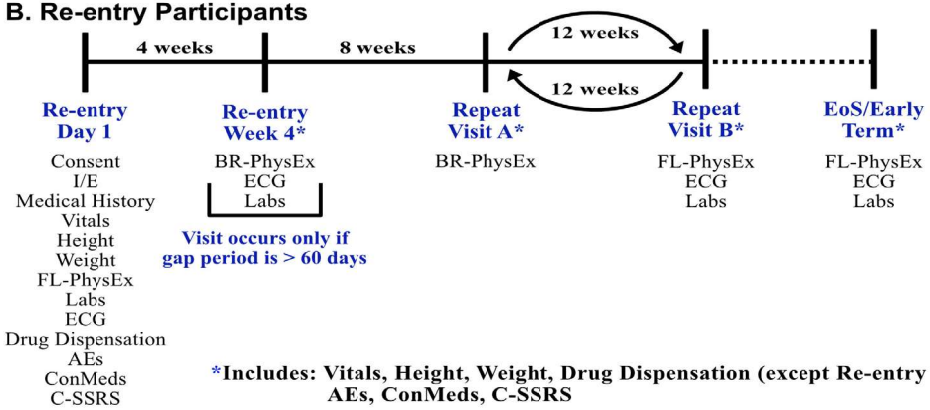
15. APPENDIX A – STUDY DESIGN SCHEMATIC

A. Active Participants



***Includes: Vitals, Height, Weight, Drug Dispensation (EoS/ET), Drug Accountability, AEs, ConMeds, C-SSRS**

B. Re-entry Participants



***Includes: Vitals, Height, Weight, Drug Dispensation (except Re-entry Week 4 and EoS/ET), Drug Accountability, AEs, ConMeds, C-SSRS**

16. APPENDIX B – SCHEDULE OF EVENTS FOR ACTIVE PARTICIPANTS

STUDY PROCEDURE	Study Day 1 [a]	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Repeat Visit A [e]	Repeat Visit B [f]	End of Study / Early Term
Informed Consent	X											
Vital Signs	X [b]	X	X	X	X	X	X	X	X	X	X	X
Height & Weight	X [b]	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X [b c]	*	*	*	X [c]	*	*	*	X [c]	*	X [c]	X [c]
Chemistry, Hematology, Urinalysis	X [b]		X		X		X		X		X	X
ECG	X [b]		X		X		X		X		X	X
Drug Dispensation [d]	X	X	X	X	X	X	X	X	X	X	X	
Drug Accountability		X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X [b]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X [b]	X	X	X	X	X	X	X	X	X	X	X
C-SSRS – Since Last Visit	X [b]	X	X	X	X	X	X	X	X	X	X	X

* Brief physical exam.

[a] Study Day 1 will take place during the Month 24 Visit for study PTI-125-04.

[b] Data collected at Month 24 Visit for study PTI-125-04 will be used.

[c] Full physical examination at Day 1 (as part of Month 24 Visit from study PTI-125-04), Week 48, Week 96, and Repeat Visit B, and at End of Study or Early Term Visit.

[d] Drug will be dispensed at Study Day 1 and every 12 weeks.

[e] Repeat Visit A occurs 12 weeks following the Week 96 visit and then reoccurs every 24 weeks thereafter.

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

17. APPENDIX C – SCHEDULE OF EVENTS FOR RE-ENTRY PARTICIPANTS

STUDY PROCEDURE	Re-entry Day 1	Re-entry Week 4 [e]	Repeat Visit A [c]	Repeat Visit B [d]	End of Study / Early Term
Informed Consent	X				
Medical History	X				
Inclusion/Exclusion Criteria	X				
Vital Signs	X	X	X	X	X
Height & Weight	X	X	X	X	X
Physical Examination	X [a]	*	*	X[a]	X [a]
Chemistry, Hematology, Urinalysis	X	X		X	X
ECG	X	X		X	X
Drug Dispensation [b]	X		X	X	
Drug Accountability		X	X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
C-SSRS – Since Last Visit	X	X	X	X	X

* Brief physical exam.

[a] Full physical examination at Re-entry Day 1, Repeat Visit B, and at End of Study or Early Term Visit.

[b] Drug will be dispensed at Re-entry Day 1 and every 12 weeks thereafter.

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

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

[e] Re-entry Week 4 visit only for subjects who completed the PTI-125-09 study >60 days prior to completing Re-entry Day 1.