Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Simufilam (PTI-125)

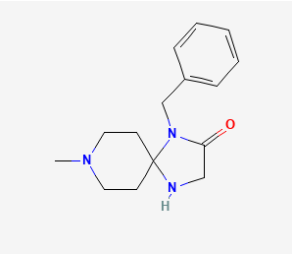
Evidence Summary

Simufilam treatment improved CSF biomarkers in an open-label phase 2a study in Alzheimer's patients, but the phase 2b trial failed to meet its primary endpoint. The US Department of Justice has opened a criminal investigation into whether Cassava Sciences, the company developing simufilam, has manipulated research results.

Neuroprotective Benefit: Although the open-label phase 2a study in Alzheimer's patients suggested improvements in CSF biomarkers, the double-blind randomized controlled phase 2b study failed to meet the primary endpoint. There are two phase 3 trials as well as two open-label studies ongoing.

Aging and related health concerns: No studies have tested simufilam for age-related diseases beyond neurodegenerative diseases.

Safety: Press releases have noted that simufilam treatment was safe and well-tolerated in phase I, phase 2a, and phase 2b studies, as well as in an open-label study, but details of the frequencies and types of adverse events have not been reported.

Availability: Not available; under development	**Dose**: In clinical trials, 50 mg or 100 mg twice daily, orally, have been tested.	**Chemical formula:** $C_{15}H_{21}N_3O$ **MW:** 259.35  Source: PubChem
Half-life: Plasma half-life is 4.5 hours	**BBB**: Penetrant (in animals)	
Clinical trials: The phase 2a and 2b studies enrolled 13 and 64 patients, respectively.	**Observational studies**: None	

What is it?

PTI-125, also known as simufilam, is a small molecule that binds to filamin A (FLNA), a scaffolding protein and regulator of the actin cytoskeleton (Cassava Sciences Inc.). PTI-125 restores the normal shape and function of altered FLNA. PTI-125 is currently under development by Cassava Sciences Inc. (previously Pain Therapeutics) for the treatment of Alzheimer's disease. Several clinical trials are ongoing in Alzheimer's patients, including two phase 3 trials.

However, there are several ongoing investigations on Cassava Sciences Inc. as well as the data related to PTI-125. Citizen petitions against Cassava Sciences were filed in August 2021, requesting the FDA to halt the ongoing clinical trials testing PTI-125, based on "allegations of manipulated Western blot images and fraudulent laboratory biomarker data" (StatNews.com). In February 2022, the FDA turned down this request on procedural grounds, noting that the requests "are not the appropriate subject of a citizen petition" (FDA response letter). In November 2021, the Securities and Exchange Commission (SEC) started an investigation into claims that Cassava Sciences manipulated research data on PTI-125/simufilam (Wall Street Journal). In July 2022, the US Department of Justice opened a criminal investigation into Cassava Sciences over whether the company manipulated research results related to PTI-125/simufilam (Reuters.com). Several peer-reviewed journal articles authored by a Cassava employee and its academic collaborators have been retracted, and for a few others, a subsequent "Expression of Concern" have been published by the journals (AlzForum.org; Piller 2022).

Neuroprotective Benefit: Although the open-label phase 2a study in Alzheimer's patients suggested improvements in CSF biomarkers, the double-blind randomized controlled phase 2b study failed to meet the primary endpoint. There are two phase 3 trials as well as two open-label studies ongoing.

Types of evidence:

- Phase 1 studies in healthy adults
- Phase 2a open-label clinical trial in patients with mild to moderate AD
- Phase 2b double-blind randomized controlled study in patients with mild to moderate AD
- 1 post-mortem study
- 2 preclinical studies

***Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function*:**
None available.

***Human research to suggest benefits to patients with dementia*:**
In the brains from patients with Alzheimer's disease and frontotempoeral dementia with parkinsonism linked to chromosome 17 (FTDP-17), FLNA was colocalized with fibrillary tau protein (Feuillette et al, 2010).

On September 9, 2019, Cassava Sciences announced the results of a 28-day open-label phase 2a study of PTI-125 (100 mg bid) in 13 individuals with mild-to-moderate Alzheimer's disease (press release; Wang et al., 2020). Changes in cerebral spinal fluid (CSF) measures from baseline were the following:

- Decreased total tau by 20% ($p<0.001$)
- Decreased p-tau181 by 34% ($p<0.0001$)
- Decreased neurofilament light chain (NfL; a marker of neurodegeneration) by 22% ($p<0.0001$)
- Decreased neurogranin (a marker of synaptic loss) by 32% ($p<0.0001$)
- Decreased YKL-40 (a marker of inflammation) by 9% ($p<0.0001$)
- Decreased IL-6 (a marker of inflammation) by 14% ($p<0.0001$)
- Decreased IL-1β (a marker of inflammation) by 11% ($p<0.0001$)
- Decreased TNFα (a marker of inflammation) by 5% ($p=0.001$)
- Improved ratio of CSF p-tau/Aβ (a marker of Alzheimer's disease) ($p<0.001$)

Target engagement was demonstrated in patients' lymphocytes by a shift in FLNA conformation from aberrant to native: 93% was aberrant on Day 1 vs. 40% on Day 28 (press release; Wang et al., 2020). PTI-

125 significantly reduced FLNA linkages with α7-nicotinic acetylcholine receptor (α7nAChR) and toll-like receptor 4 (TLR-4), and reduced binding of Aβ42 to both α7nAChR and CD14, the co-receptor for TLR-4.

On May 15, 2020, Cassava Sciences announced the top-line results from the phase 2b double-blind randomized controlled study of PTI-125 (50 or 100 mg twice daily for 28 days) in patients with mild to moderate Alzheimer's disease (press release). The primary endpoint was change from baseline in CSF levels of tau and other biomarker assessments, but the study failed to show a statistically significant effect of PTI-125 in these biomarkers. PTI-125 treatment significantly reduced a secondary endpoint, CSF levels of IL-1β ($p<0.035$), a biomarker of neuroinflammation, from baseline to Day 28. A post-hoc analysis of biomarker data revealed high variability in CSF biomarker levels. The company noted that the PTI-125 treatment effects may have been masked by the high variability in biomarker levels.

On August 3, 2022, Cassava Sciences announced results of an interim analysis on an open-label study (press release). An interim analysis was performed on the first 100 patients who completed at least 12 months of open-label treatment with PTI-125 (100 mg, twice daily). Overall, a cognitive score (ADAS-Cog11) improved by 1.5 points ($p<0.05$), with 63% of patients showing an improvement. Because of the open-label design of this study without a placebo control, results need to be interpreted with caution, as improvements in cognitive scores could be due, in part, to practice effects.

There are 2 randomized double-blind placebo-controlled phase 3 trials that are currently ongoing, testing the safety and efficacy of PTI-125 treatment (50 mg or 100 mg, twice daily) in patients with mild to moderate Alzheimer's disease (NCT05026177; NCT04994483). These studies are scheduled to be completed in October 2023 and June 2024.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
A mouse model of familial Alzheimer's disease (PS1 mutation) had increased expression of FLNA in the hippocampus (Lu et al, 2010), and cell culture studies suggest that stimulation of α7nAChR or treatment of cells enriched with α7nAChR with Aβ42 induced tau phosphorylation (Wang et al, 2003).

Wang et al (2012) reported that intracerebroventricular (ICV) infusion of Aβ42 increased the association of FLNA with the α7nAChR and TLR4, and subsequently increased the expression of p-tau. These associations were reduced by co-administration with PTI-125. Similar results were seen in Alzheimer's postmortem tissue, with increased association of FLNA with α7nAChR and TLR4 and reduced association after PTI-125 administration. The association of FLNA with α7nAChR and TLR4 were reported to be due to an alteration in its conformation (determined by a change in its isoelectric point). Since the

publication of this report by Wang et al., 2012, an Erratum and an Expression of Concern were published in December 2021 and January 2022, respectively, regarding concerns about immunostaining and Western blots included in this study. The journal (Journal of Neuroscience) is awaiting the outcome of an investigation by the academic authorities at the City University of New York (CUNY) before taking further action.

PTI-125 binds to FLNA at femtomolar concentration in Alzheimer's postmortem tissue versus picomolar concentration in the control post-mortem tissue and displaces naloxone, which was previously shown to bind to FLNA, restoring FLNA to its native form (measured by a change in its isoelectric point)(Wang et al, 2017). PTI-125 also restored FLNA to its native form in Alzheimer's mice and mice with ICV injections of Aβ42. Administration of PTI-125 for two months in young or aged mouse models of Alzheimer's disease reduced the association of FLNA with α7nAChR, and reduced p-tau, beta-amyloid, and inflammatory cytokines. PTI-125 also improved NMDA receptor function, insulin signaling, and increased synaptic density. PTI-125 also improved spatial memory in old mice and working memory in young mice. PTI-125 reduced the association of FLNA with α7nAChR in postmortem Alzheimer's tissue and prevented beta-amyloid-induced tau phosphorylation in postmortem control tissue. Since the publication of this report, an Expression of Concern was published by the journal in May 2022, noting that the editors are aware of concerns regarding this publication. Although the editors did not find compelling evidence of data manipulation intended to misrepresent the results, other errors were identified in the publication in the course of the evaluation. The journal is aware of an ongoing inquiry of related concerns by the sponsoring institution (CUNY) and will make a final decision on the appropriate corrective action upon completion of the inquiry.

APOE4 interactions: Unknown

Aging and related health concerns: No studies have tested simufilam for age-related diseases beyond neurodegenerative diseases.

Safety: Press releases have noted that simufilam treatment was safe and well-tolerated in phase I, phase 2a, and phase 2b studies, as well as in an open-label study, but details of the frequencies and types of adverse events have not been reported.

Types of evidence:

- Phase 1 studies in healthy adults
- Phase 2a open-label clinical trial in patients with mild to moderate AD
- Phase 2b double-blind randomized controlled study in patients with mild to moderate AD
- Two preclinical studies

In an open-label phase 2a study in 13 individuals with mild-to-moderate Alzheimer's disease, PTI-125 treatment (100 mg, twice daily, orally) for 28 days was described as safe and well-tolerated in all patients (press release; Wang et al., 2020). Details of the frequencies and types of adverse events were not included in the published report or the press release. Plasma half-life was 4.5 hours and approximately 30% drug accumulation was observed on Day 28 compared to Day 1.

In a phase 2b double-blind randomized controlled study in 64 patients with mild to moderate Alzheimer's disease, PTI-125 treatment (50 or 100 mg twice daily) for 28 days was described as safe and well-tolerated (press release). Though details of the frequencies and types of adverse events were not included in the press release.

In an ongoing open-label study, interim analysis on the first 100 patients who completed at least 12 months of PTI-125 treatment (100 mg, twice daily) reported that the drug appears safe and well-tolerated (press release). However, details of the frequencies and types of adverse events were not included in the press release.

Drug interactions: Not currently known.

Sources and dosing: In Alzheimer's patients, 50 mg and 100 mg, orally, twice daily, have been investigated.

Research underway: There are currently 4 clinical trials testing PTI-125, based on ClinicalTrials.gov. One is a phase 2, 96-week, open-label extension of PTI-125 in mild to moderate Alzheimer's patients (NCT05352763). This study is expected to be completed in November 2025. There is another phase 2 study ongoing which is a 12-month open-label study of PTI-125 treatment (100 mg, twice daily) followed

by a 6-month randomized withdrawal and a 6-month open-label treatment (NCT04388254). This study is estimated to be completed in July 2023. There are two randomized double-blind placebo-controlled phase 3 trials ongoing that are testing the safety and efficacy of PTI-125 treatment (50 mg or 100 mg, twice daily) in patients with mild to moderate Alzheimer's disease (NCT05026177; NCT04994483). Based on a press release from August 3, 2022, over 400 patients have been enrolled in the phase 3 studies. These studies are scheduled to be completed in October 2023 and June 2024.

There are also several investigations on Cassava Sciences that are ongoing by the Department of Justice, the SEC, and journals that published work related to PTI-125/simufilam.

Search terms:

- PTI-125
- Simufilam
- Filamin + alzheimer
- Filamin A [review]

Websites:

- Clinicaltrials.gov
- NIH RePORTER
- Pubmed
- Pubchem
- Drugbank.ca (0)