



Cassava Sciences Reports Positive Phase 2a Clinical Results in Alzheimer's Patients

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Lead drug candidate, PTI-125, significantly decreased key biomarkers of neuroinflammation and neurodegeneration in all study patients (p<.001)

Clinical data support initiation of a Phase 2b study in Alzheimer's in Q3 2019

AUSTIN, Texas, Sept. 09, 2019 (GLOBE NEWSWIRE) -- Cassava Sciences, Inc. (Nasdaq: SAVA), a biopharmaceutical company, today reported positive top-line clinical results of its lead drug candidate for Alzheimer's disease, PTI-125. The Alzheimer's brain is characterized by a misfolded protein called Filamin A (FLNA); PTI-125 binds to FLNA and restores its normal shape and function. In a Phase 2a study funded by the National Institutes of Health (NIH), treatment with PTI-125 for 28 days significantly reduced biomarkers of Alzheimer's disease pathology, neuroinflammation and neurodegeneration in patients.

"Based on these encouraging biomarker results, this new treatment could be an important part of the research dialogue in Alzheimer's disease," said **Dr. Jeffrey Cummings**, Research Professor of the Department of Brain Health, UNLV and Director of the Center for Neurodegeneration and Translational Neuroscience of the Cleveland Clinic Lou Ruvo Center for Brain Health. "This drug candidate appears to target some of the more toxic components of the illness. Results will need to be replicated in larger studies to prove it's a definitive advance in the field."

The Phase 2a study achieved a 100% responder rate, with all patients responding to PTI-125. A key objective of this first-in-patient study was to measure drug effects on biomarkers in the brain (i.e., in cerebrospinal fluid, or CSF) before and after 28 days of treatment with PTI-125.

Key results include:

- Total tau (T-tau) decreased 20% (p<.001)
- Phosphorylated tau (P-tau) decreased 34% (p<.0001)
- Neurofilament light chain (NfL), a marker for neurodegeneration, decreased 22% (p<.0001)
- Neurogranin, a marker for cognitive decline, decreased 32% (p<.0001)
- Neuroinflammatory marker YKL-40, an indicator of microglial activation, decreased 9% (p<.0001)
- Proinflammatory Interleukin 6 (IL-6) decreased 14% (p<.0001)
- Proinflammatory Interleukin 1 beta (IL-1 β) decreased 11% (p<.0001)
- Proinflammatory Tumor necrosis factor alpha (TNF α) decreased 5% (p=.001)
- The ratio of CSF P-tau to A β ₄₂, a widely accepted biochemical value of Alzheimer's disease, improved in all evaluable patients (p<.001).

"We conclude from this study that PTI-125 was able to reduce biomarkers of neurodegeneration and neuroinflammation in Alzheimer's patients at a dose that appears safe and well-tolerated," said Nadav Friedmann, PhD, MD, Chief Medical Officer of Cassava Sciences. "To our knowledge, no other drug has shown such promising results on objective, validated biomarkers of disease."

Cognition was not assessed in this first-in-patient study; however, published studies show that elevated levels of CSF biomarkers P-tau and total tau/A β ₄₂ ratio correlate with deficiencies on a range of memory and sustained attention assessments.

"We are excited to lead the way in the effort to bring a new treatment paradigm to Alzheimer's, a disease that has seen few scientific advancements to date despite massive research efforts," said Remi Barbier, President & CEO of Cassava Sciences. "The relationship between biomarkers and Alzheimer's disease is crucial, well-known and widely published. As a result, we're cautiously optimistic that PTI-125 moves us closer towards the goal of a disease-modifying treatment. And as always, we are grateful for the support of our collaborators, advisors and NIH, whose peer-review system of evaluation has enabled us to advance PTI-125 step-wise from basic research to clinical testing within 10 years."

Next Step: Initiation of a Phase 2b Study in Q3 2019

Based on these positive Phase 2a results, Cassava Sciences plans to initiate a Phase 2b study of PTI-125. This Phase 2b study will also be funded by NIH. A key objective of the Phase 2b study will be to replicate the beneficial effects of PTI-125 on biomarkers of Alzheimer's disease in a larger, blinded study. Phase 2b is designed as a blinded, randomized, placebo-controlled, multicenter, dose-response, research study in approximately 60 patients with mild-to-moderate Alzheimer's disease. Study patients will be dosed with PTI-125 100 mg, 50 mg, or matching placebo, twice daily for 28 continuous days. The primary efficacy endpoint is improvement in biomarkers of Alzheimer's disease. Enrollment is expected to take approximately 12 months.

Phase 2a Study Design

Phase 2a was a first-in-patient, open-label, multi-center, safety, pharmacokinetic and biomarker study of PTI-125 in the U.S. Thirteen patients with mild-to-moderate Alzheimer's disease, age 50-85, received 100 mg oral PTI-125 twice daily for 28 days. A diagnosis of Alzheimer's disease was confirmed with Mini-Mental State Examination (MMSE) ≥ 16 and ≤ 24 and a CSF T-tau/A β ₄₂ ratio ≥ 0.30 . Safety was assessed by ECGs, clinical labs, adverse event monitoring and physical examinations. CSF was drawn from patients before dosing started and again after 28 continuous days of

dosing with PTI-125. CSF samples were then analyzed for biomarkers of Alzheimer's pathology (T-tau, P-tau, A β ₄₂); neurodegeneration (NfL, neurogranin); and neuroinflammation (YKL-40, IL-6, IL-1 β and TNF α). A consulting *biostatistician* conducted an independent analysis of the data set.

Cassava Sciences expects to present a full data set from this Phase 2a study at *Clinical Trials on Alzheimer's Disease* (CTAD), a conference for the medical and scientific community being held in San Diego, CA, December 4-7th, 2019.

Cassava Sciences' Phase 2a study was supported by the *National Institute on Aging* at NIH under award AG060878.

About PTI-125 and Cassava's Scientific Approach

The target of PTI-125 is an altered form of filamin A (FLNA), a scaffolding protein. Altered FLNA in the brain disrupts the normal function of neurons, leading to Alzheimer's pathology, neurodegeneration and neuroinflammation. Cassava's lead drug candidate, PTI-125, is a small molecule drug that restores the normal shape of FLNA in the brain. This action improves the function of certain receptors in the brain and exerts powerful anti-neuroinflammatory effects.

Cassava Sciences is also developing a biomarker/diagnostic to detect Alzheimer's disease with a simple blood test. This program, called PTI-125Dx, also receives significant scientific and financial support from NIH.

The underlying science for Cassava Sciences' programs in neurodegeneration is published in several prestigious peer-reviewed technical journals, including *Journal of Neuroscience*, *Neurobiology of Aging*, and *Journal of Biological Chemistry*. As previously announced, in 2018 NIH awarded Cassava two research grants following an in-depth, confidential review of its science and technology. These two NIH grants represent up to \$6.7 million of non-dilutive financing.

About Alzheimer's Disease

Alzheimer's disease is a progressive brain disorder that destroys memory and thinking skills. Currently, there are no drug therapies to halt Alzheimer's disease, much less reverse its course. In the U.S. alone, approximately 5.8 million people are currently living with Alzheimer's disease, and approximately 487,000 people age 65 or older will develop Alzheimer's in 2019. ¹ The number of people living with Alzheimer's disease is expected to grow dramatically in the years ahead due to an aging population, which may also result in growing social and economic burden of Alzheimer's. ²

^{1, 2} Source: Alzheimer's Association. 2019 Alzheimer's Disease Facts and Figures. Available online at: <https://www.alz.org/media/documents/alzheimers-facts-and-figures-2019-r.pdf>

About Cassava Sciences, Inc.

The mission of Cassava Sciences is to detect and treat neurodegenerative diseases, such as Alzheimer's disease. Over the past ten years, Cassava Sciences has combined state-of-the-art technology with new insights in neurobiology to develop novel solutions for Alzheimer's disease.

Cassava Sciences owns worldwide development and commercial rights to its research programs in Alzheimer's disease, and related technology, without royalty obligations to any third-party.

Declared Interest. Dr. Cummings is a paid consultant for Cassava Sciences.

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Source: Cassava Sciences, Inc.