Cassava Announces Publication of Peer-Reviewed Phase 3 Results for Simufilam in Alzheimer's Disease in the Journal of Prevention of Alzheimer's Disease

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As previously disclosed, the studies did not meet pre-specified co-primary, secondary, or exploratory biomarker endpoints

The paper provides a detailed analysis of the RETHINK-ALZ and REFOCUS-ALZ studies and confirms simufilam's favorable safety profile in these studies

Exploratory post-hoc analyses offer informative insights

AUSTIN, Texas, Jan. 13, 2026 (GLOBE NEWSWIRE) -- Cassava Sciences, Inc. (NASDAQ: SAVA, "Cassava", the "Company"), a biotechnology company focused on developing novel, investigational treatments for central nervous system (CNS) disorders such as Tuberous Sclerosis Complex (TSC)-related epilepsy, today announced publication of the article *Phase 3 randomized clinical trials of simufilam in mild-to-moderate Alzheimer's disease* in an upcoming issue of the Journal of Prevention of Alzheimer's Disease (JPAD). The paper provides a detailed analysis of data from two Phase 3 clinical trials, RETHINK-ALZ and REFOCUS-ALZ. While, as previously disclosed, the two studies did not meet their pre-specified co-primary, secondary, or exploratory biomarker endpoints, exploratory post-hoc analysis of the studies offers informative insights. The paper is publicly available on the JPAD website: https://www.sciencedirect.com/science/article/pii/S2274580725004108.

Topline results of RETHINK-ALZ (NCT04994483), which randomized 804 people with mild to moderate Alzheimer's disease, were originally reported in November 2024, and topline results from REFOCUS-ALZ (NCT05026177), which randomized 1,125 patients, were reported in March 2025. As previously disclosed, the Company has discontinued development of, and plans no further investment in, the Alzheimer's disease program.

"In keeping with our commitment to report the detailed results, we are pleased to make the data from the RETHINK-ALZ and REFOCUS-ALZ studies available to the Alzheimer's disease scientific community through publication in the highly respected Journal of Prevention of Alzheimer's Disease. We hope the paper can serve as a foundation for further research in the field," said **Rick Barry, President and Chief Executive Officer** of Cassava. "The detailed safety observations reported in the article provide heartening encouragement for our ongoing development program in TSC-related epilepsy, as we work to initiate a proof-of-concept study in collaboration with leading investigators."

Exploratory Findings

Although the trials failed to meet their co-primary, secondary, and exploratory biomarker endpoints, some prespecified secondary endpoints and post hoc hypothesis-generating analyses showed potential treatment differences between the higher dose of simufilam and placebo in the predefined mild subgroup (mini-mental state exam (MMSE) score 21-27) on the 12-item Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog12), including:

- **Mild Patients in REFOCUS-ALZ**: Simufilam (100 mg) was associated with slower cognitive decline than placebo in the prespecified mild subgroup, with differences at Week 4 and Weeks 28, 40, 52, and 64 (nominally significant at $p = 0.01$, 0.01, 0.02, 0.02, and 0.02, respectively). This potential treatment difference did not replicate in RETHINK-ALZ and was no longer evident at Week 76 of REFOCUS-ALZ (which had 45% missing data due to early study termination).
- **Pooled Mild Patients in REFOCUS-ALZ and RETHINK-ALZ:** A prespecified pooled analysis of mild patients administered simufilam (100 mg) or placebo in both trials through week 52 showed potential treatment group differences at weeks 4 and 28 (nominally significant at $p < 0.01$). An exploratory post hoc analysis of the pooled mild subgroups using a plasma p-tau181 cutoff of ≥ 67 (the highest half of all patients) showed a difference in the slowing of decline at Weeks 4, 28, and 40 (nominally significant at $p = 0.03$, 0.001, 0.006, respectively), with a trend at Week 52 ($p = 0.066$).

These clinical trials were the first Phase 3 Alzheimer's disease studies to rely primarily on a plasma biomarker (p-tau181) for biological confirmation of disease. The authors of the paper observed that an amyloid PET (positron emission tomography) sub-study in REFOCUS-ALZ showed that 21% of participants (33 of 160) were unexpectedly amyloid negative at baseline, indicating an absence of Alzheimer's disease pathology. This suggests that the plasma p-tau181 assay cut-off used as an entry criterion in both trials was insufficient to screen effectively for Alzheimer's disease pathology in trial participants.

James Kupiec, MD, Retired Chief Medical Officer of Cassava and primary publication author, commented, "Exploratory and post hoc analyses identified specific subgroups of patients with an observed treatment difference between the higher dose of simufilam and placebo. While Cassava does not intend to conduct further studies in this indication, we believe these observations are informative. We have made our data and analyses accessible through JPAD with the hope that this paper can serve as a valuable resource for the Alzheimer's community's mission to improve patient care."

Dr. Anton Porsteinsson, Director of the University of Rochester's Alzheimer's Disease Research, Care and Education Program, commented, "I am very pleased that the results of the REFOCUS-ALZ and RETHINK-ALZ studies have been meticulously written and peer reviewed. Publication of

the results from these large, rigorously designed and conducted Phase 3 studies plays an essential role in shaping future studies and ensuring a complete scientific record for the betterment of drug development and public health."

Overview of the RETHINK-ALZ and REFOCUS-ALZ Studies

The Phase 3 RETHINK-ALZ (NCT04994483) and REFOCUS-ALZ (NCT05026177) trials were designed as multi-center, double-blinded, placebo-controlled, randomized parallel group studies to evaluate the safety and efficacy of simufilam compared to placebo across distinct clinical sites in the U.S., Canada, and Asia.

The prespecified co-primary endpoints for the studies included the change in cognition and function from baseline to the end of the double-blind treatment period, assessed by the ADAS-Cog12 and ADCS-ADL scales, comparing simufilam to placebo. Secondary endpoints included several well validated measures of neuropsychiatric symptoms and caregiver burden. Safety was evaluated by adverse event monitoring, as well as standard laboratory and ECG assessments. REFOCUS-ALZ also included an evaluation of changes in plasma and cerebrospinal fluid biomarkers as well as an evaluation of MRI and PET scans.

About Simufilam

Simufilam is a proprietary, investigational oral small molecule believed to modulate activity of the filamin A protein, which regulates diverse aspects of neuronal development[1].

About Cassava Sciences, Inc.

Cassava Sciences, Inc. (NASDAQ: SAVA), is a biotechnology company focused on developing novel, investigational treatments, including simufilam, for central nervous system disorders, such as tuberous sclerosis complex (TSC)-related epilepsy, and potentially other indications. Simufilam is a proprietary, investigational oral small molecule believed to modulate activity of the filamin A protein, which regulates diverse aspects of neuronal development[1]. The Company is planning a Phase 2 proof-of-concept study to evaluate simufilam in patients with TSC-related epilepsy, collaborating closely with the TSC Alliance and key opinion leaders. The program is based on a method of treatment patent issued in 2025 and in-licensed from Yale University. Cassava is based in Austin, Texas.

For more information, please visit: https://www.CassavaSciences.com

References:

1. *Zhang L, Bartley CM, Gong X, Hsieh, LS.; LinTV, Feliciano DM, Bordey A. "MEK-ERK1/2-Dependent FLNA Overexpression Promotes Abnormal Dendritic Patterning in Tuberous Sclerosis Independent of mTOR. Neuron (2014) 84 (1), 78-91. DOI: 10.1016/j.neuron.2014.09.009*

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Cautionary Note Regarding Forward-Looking Statements: add a few notes on the paper

This news release contains forward-looking statements that may include but are not limited to statements regarding the implications of safety observations in the REFOCUS-ALZ and RETHINK-ALZ studies for the Company's ongoing development program in TSC-related epilepsy and the potential for the observations in the published paper to contribute to Alzheimer's disease research. Forward-looking statements may be identified by words such as "anticipate", "before", "believe", "could", "expect", "forecast", "intend", "may", "pending", "plan", "possible", "potential", "prepares for", "will", and other words and terms of similar meaning.

Such statements are based on our current expectations and projections about future events. Such statements speak only as of the date of this news release and are subject to a number of risks, uncertainties and assumptions, including, but not limited to, those risks inherent in drug discovery and development or specific to Cassava Sciences, Inc., as described in the section entitled "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2024 and Quarterly Report on Form 10-Q for the period ended September 30, 2025, and subsequent reports periodically filed and to be filed with the SEC. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from expectations in any forward-looking statement. In light of these risks, uncertainties and assumptions, the forward-looking statements and events discussed in this news release are inherently uncertain and may not occur, and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Accordingly, you should not rely upon forward-looking statements as predictions of future events. Except as required by law, we disclaim any intention or responsibility for updating or revising any forward-looking statements. For further information regarding these and other risks related to our business, investors should consult our filings with the SEC, which are available on the SEC's website at www.sec.gov.

All of our pharmaceutical assets under development are investigational product candidates. These have not been approved for use in any medical indication by any regulatory authority in any jurisdiction and their safety, efficacy or other desirable attributes, if any, have not been established in any patient population. Consequently, none of our product candidates is approved or available for sale anywhere in the world.

Our clinical results from earlier-stage clinical trials or preclinical studies may not be indicative of future results from later-stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or any scientific data we present or publish.

We are in the business of new drug discovery and development. Our research and development activities are long, complex, costly and involve a high degree of risk. Holders of our common stock should carefully read our Annual Report on Form 10-K and subsequent Quarterly Reports on Form 10-Q and any other SEC filings in their entirety, including the risk factors therein. Because risk is fundamental to the process of drug discovery and development, you are cautioned to not invest in our publicly traded securities unless you are prepared to sustain a total loss of the money you have invested.

Source: Cassava Sciences, Inc.