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**VIA FEDEX**

Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
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## CITIZEN PETITION

This petition for administrative action is submitted on behalf of the undersigned Petitioner pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act to request that the Commissioner of Food and Drugs (the "Commissioner") halt two ongoing trials of the drug Simufilam (formerly PTI-125) sponsored by Cassava Sciences (NCT04388254 and NCT04994483), pending a thorough audit by the FDA of the matters described herein.

Cassava Sciences is a public company that is focused on developing therapies targeted at Alzheimer's Disease. Cassava is currently sponsoring clinical trials NCT04388254 and NCT04994483 for its proprietary drug Simufilam, which is claimed to represent a novel approach to Alzheimer's treatment. In its recent SEC filings and elsewhere, the company has publicly announced the successful completion of its End of Phase 2 meeting for Simufilam with the FDA, and stated that the company and the FDA are aligned on key elements of a Phase 3 clinical program. The company has stated that it expects to initiate its Phase 3 program with Simufilam in September 2021.

Information available to the petitioner, however, which is summarized below and detailed in the enclosed technical report, raises grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy. Petitioner is therefore requesting the FDA to halt the clinical studies pending a thorough audit of the publications and data relied on by Cassava in support of its claims.

## I. ACTION REQUESTED

Petitioner is requesting that the FDA halt the current clinical studies of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT04388254 and NCT04994483), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the IND application for Simulifam's use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease. Petitioner is further requesting that the FDA oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease. The ongoing clinical trials should be paused until the satisfactory completion of these investigations.

## II. STATEMENT OF GROUNDS

Petitioner has enclosed with this Petition (and incorporates herein) a detailed technical report presenting multiple reasons to question the quality and integrity of the research supporting Cassava's claims about Simufilam's use for Alzheimer's Disease. In sum, that report explains:

(1) All of the foundational science supporting Cassava's claims about Simufilam's use for Alzheimer's Disease comes from a series of papers with two common co-authors (Dr. Hoau-Yan-Wang at City University of New York and Dr. Lindsay Burns of Cassava). The studies of Drs. Wang and Burns were used by Cassava to obtain NIH grants and to open an Investigational New Drug (IND) application to study Simufilam. They form the foundation for the current clinical trials of Simufilam.
(2) No other lab has confirmed Cassava's research connecting Filamin A to Alzheimer's Disease, nor has any other lab confirmed that Simufilam binds or modifies Filamin A or has effects in Alzheimer's Disease models.
(3) Close review of the data and analyses in the foundational research papers and Cassava's recent publications of clinical trial analyses presents three primary areas of concern:
    a. The underlying papers of Drs. Wang and Burns involve extensive use of Western blot analyses to support their claims connecting Simufilam to Alzheimer's. Detailed analysis of the western blots in the published journal articles shows a series of anomalies that are suggestive of systematic data manipulation and misrepresentation.
    b. Some of the foundational studies published by Drs. Wang and Burns make claims about Simufilam's effects in experiments conducted on postmortem human brain tissue. The methodology allegedly used in these experiments defies logic, and the data presented again have hallmarks of manipulation.
    c. Cassava's presentation of clinical biomarker data from the Phase 2b trials raises questions about the validity of the data. The CSF samples in this study were first analyzed by an outside lab, which found that Simufilam was ineffective in improving the primary biomarkers end point and high variability in other biomarkers. But Cassava had these samples analyzed again and this time reported that Simufilam rapidly and robustly improved a wide array of

biomarkers. Cassava has not fully published the data from this reanalysis, but a presentation poster that it published on July 26, 2021, which appears to describe aspects of that work, shows signs of data anomalies or manipulation.

(4) Six further aspects of the research by Drs. Wang and Burns are incompatible with scientific norms, and these claims raise further suspicions.
   a. Remarkably High Affinity Binding Between PTI-125 and Filamin A.
   b. Remarkably High Affinity Binding Between Naloxone and Filamin A.
   c. Isoelectric Focusing Experiments in Multiple Papers Indicate 100% of Filamin in Altered Conformation in Alzheimer's Disease and largely Restored to Correct Conformation by PTI-125.
   d. Novel Blood Diagnostic SavaDx Represents Plasma Filamin A Level
   e. PTI-125/Simufilam Improves Memory in a Mouse Model of Alzheimer's Disease.
   f. PTI-125/Simufilam Blocks the Interaction Between β-amyloid and α7- Nicotinic Acetylcholine Receptors.

Petitioner submits that the extensive evidence set forth in the enclosed report, which presents grave concerns about the quality and integrity of the scientific data supporting Cassava's claims for Simulifam's efficacy, provides compelling grounds for pausing the ongoing clinical trials until the FDA can conduct and complete a rigorous audit of Cassava's research.

## III. ENVIRONMENTAL IMPACT

Petitioner states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. Sections 25.30 and 25.31.

## IV. ECONOMIC IMPACT

Economic impact information will be submitted at the request of the Commissioner.

## V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

Jordan A. Thomas
Enclosures