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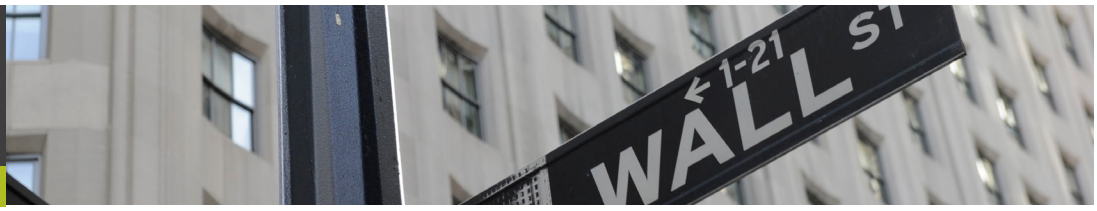

Second Supplemental Statement of Concern Regarding the Accuracy and Integrity of Clinical and Preclinical Data Supporting the Ongoing Clinical Evaluation of Compound PTI-125, Also Known As Simufilam

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Jordan A. Thomas
Labaton Sucharow LLP
140 Broadway
New York, New York 10005
(212) 907-0700 (main)
(212) 907-0836 (direct)
jthomas@labaton.com

Second Supplemental Statement of Concern Regarding the Accuracy and Integrity of Clinical and Preclinical Data Supporting the Ongoing Clinical Evaluation of Compound PTI-125, Also Known as Simufilam

SUMMARY

In my Citizen Petition and first supplemental submission, we noted concerns about possible data manipulation in both preclinical and clinical studies associated with Simufilam. In this supplemental submission, we outline five new major concerns regarding the drug's Phase 2a and Phase 2b biomarker results, arising from information identified by us and the scientific community, and from Cassava Sciences' own recent public statements

These five major concerns are:

1. Cassava claims not to have the Western blots that comprise the original data for the Phase 2a biomarker study.
2. Cassava publicly claims that the initial Phase 2b biomarker reanalysis and "redo" were performed by an "outside lab," when it appears that they were both done by Dr. Wang, whose research the company separately describes as being done "in-house."
3. Cassava publicly stated that the initial and redo analyses of the phase 2b study were done by two distinct "outside labs." In fact, the initial and the redo analyses appear to have both been done in-house by Dr. Wang. Cassava's preprint, describing the phase 2b biomarker data, contradicts the company's public statements and clarifies that Dr. Wang and his colleagues at CUNY alone conducted the biomarker redo analyses. Cassava's trial protocol submitted to ClinicalTrials.gov also states that CSF samples for the first analysis were sent to Dr. Wang for biomarker assays. If Dr. Wang did both the initial and redo analyses, this is inconsistent with Cassava's public claims that these tests were done by different outside labs.

4. Many of the results from Dr. Wang's Phase 2b redo have what appear to be data manipulation or GROSS LAB ERRORS—values incompatible with standards for these type of analyses—which raises additional questions about the validity of the biomarker results associated with the redo.
5. The Phase 2a and 2b biomarker studies were likely key elements of the Special Protocol Assessment (SPA) submitted to the FDA. If the Phase 2a or 2b studies were misrepresented, that SPA should be rescinded in accordance with applicable law and regulations.

AMENDMENTS

1. **Authenticity and Availability of Phase 2a Data—Western Blots**

Cassava's biomarker data from their Phase 2a trial was published in the 2020 The Journal of Prevention of Alzheimer's Disease (doi: 10.14283/jpad.2020.6). This clinical biomarker study relied extensively on Western blots that have been externally questioned by members of the scientific community, including the leading expert in scientific image manipulation. To validate Cassava's clinical studies, experts have requested the original Western blot films: (https://pubpeer.com/publications/A8DD7059A8A7F13D4899049A83F61E).

On September 3, 2021, Remi Barbier, Cassava's CEO, claimed in a public statement "we don't have the original films or images for the Western blots in question. Those were generated by our science collaborator at CUNY, who is Prof. Wang." However, this representation is highly doubtful. Dr. Burns, a Cassava employee and his wife, is the corresponding author for this phase 2a biomarker paper. As corresponding author, **Dr. Burns is responsible for storing, maintaining, and validating any data after publication and as a company conducting a clinical trial Cassava is responsible for storing these original phase 2a data and relevant**

records. Furthermore, Cassava is a multi-billion dollar drug development company with just one drug candidate. What are the odds that the company doesn't have any of the original data and scientific back-up for research spanning a decade? Even if this incredible representation were true, what does it say about the company and its senior leadership that they don't have this standard scientific back-up? Moreover, with the integrity of his company, personnel and research being called into question, why haven't Mr. Barbier and his team gone to CUNY and secured the evidence necessary to quickly resolve these concerns, rather than simply trying to push pace on the company's planned clinical trials?

2. **Phase 2b Biomarker Redo Was Not Done by an "Outside Lab"**

In its September 14, 2020 press release and 2020 Form 10-K at page 12, Cassava stated that the redo was conducted by an "outside lab." Contrary to these public statements and filings, the Research Square preprint (https://www.researchsquare.com/article/rs-249858/v1) documenting Cassava's redo analysis states that the experiments were done by Dr. Wang and associates at CUNY. How can Dr. Wang's lab accurately be referred to as an "outside lab" when Cassava has no laboratory facilities, CUNY and Wang are the company's scientific collaborators, Dr. Wang has been the lead scientist on virtually all Simufilam related research for the company over the last decade, Dr. Wang has been described as a paid consultant to the company in his research papers (papers Barbier and other Cassava employees are listed as authors) and in the company's public presentations, and Dr. Wang is a member of Cassava's scientific advisory board?

Furthermore, in press releases and their form 8-K filing (https://www.marketwatch.com/investing/stock/sava/SecArticle?guid=14882421), Cassava has

repeatedly stated that "Simufilam and SavaDx were both developed in-house." Again, how can Dr. Wang's "in-house" research accurately be referred to as work done by an "outside lab"?

3. **Which Outside Lab Did the First Phase 2b Biomarker Study?**

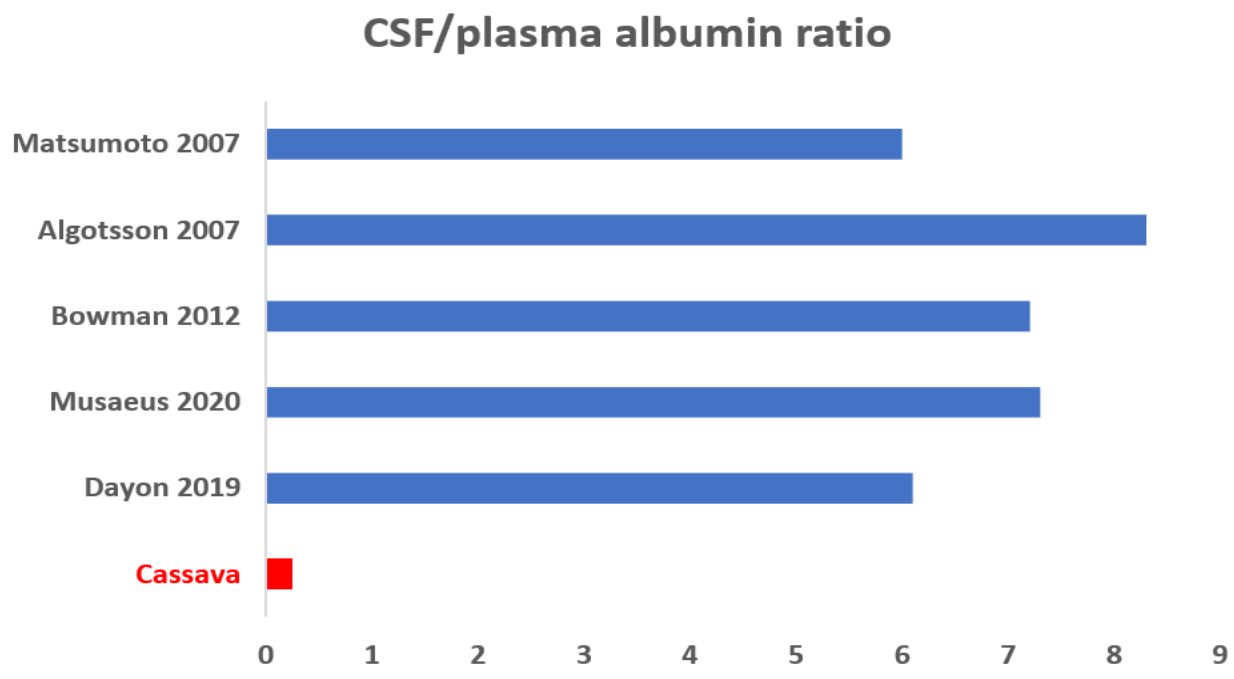
In its September 14, 2020 press release (https://www.globenewswire.com/news-release/2020/09/14/2092861/0/en/Cassava-Sciences-Announces-Final-Results-of-a-Phase-2b-Clinical-Study-of-Sumifilam-in-Patients-with-Alzheimer-s-Disease.html), Cassava stated that "initial bioanalysis [was done] by a different lab" than the redo. As documented above, the redo was done by Dr. Wang.

To date, Cassava has never named the "outside" lab that performed the initial biomarker analysis. According to the protocol filed on ClinicalTrials.gov (available at https://clinicaltrials.gov/ProvidedDocs/03/NCT04079803/Prot_000.pdf), **the first analysis may also have been done by Dr. Wang**. Specifically, Section 7.3.4 ("CSF assays") states: CSF samples should be split, with 2.5 mL shipped to Dr. Wang at CUNY and, for Day 28 only, an additional 0.5 mL shipped to Worldwide Clinical Trials (WCT). This 0.5 mL sample will be assayed for the PTI-125 analyte at WCT using a qualified assay. The remaining 2.5 or 2 mL will be retained at the study site frozen at -20°C or below until informed by the Sponsor. The samples collected at screening and on Study Day 28 will be shipped frozen on dry ice (Monday – Wednesday) to **Dr. Hoau-Yan Wang, CUNY School of Medicine, SOM CDI 3370, 85 St. Nicolas Terrace, New York, NY 10027 to be tested in biomarker assays including: Abeta; Tau, ptau; YKL40; IL-6, TNFα and IL-1β; Neurogranin; Neurofilament light chain**." If Dr. Wang did both the initial analysis and redo, as this newly discovered evidence suggests, this would be inconsistent with Cassava's prior public claims that the first was done by a different lab and raises new red flags about the company's research.

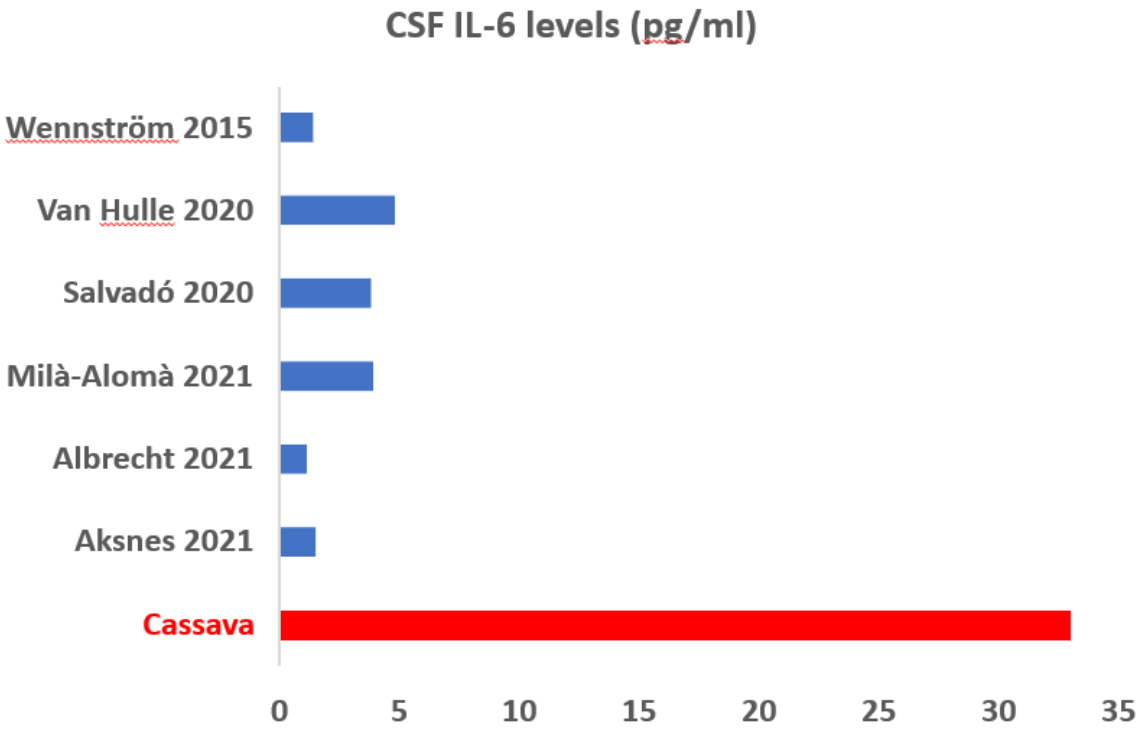
4. Likely Lab Errors or Manipulation in the Phase 2b Redo Study

The Phase 2b redo was conducted by Dr. Wang and used both Western blotting and other immunoassays. Of the ten biomarkers analyzed, it seems the baselines for three are far outside expectations. As these baselines are mean averages from 60+ patients, their extreme variation from many other Alzheimer's Disease (AD) biomarker studies suggests the redo has major lab errors or manipulation.

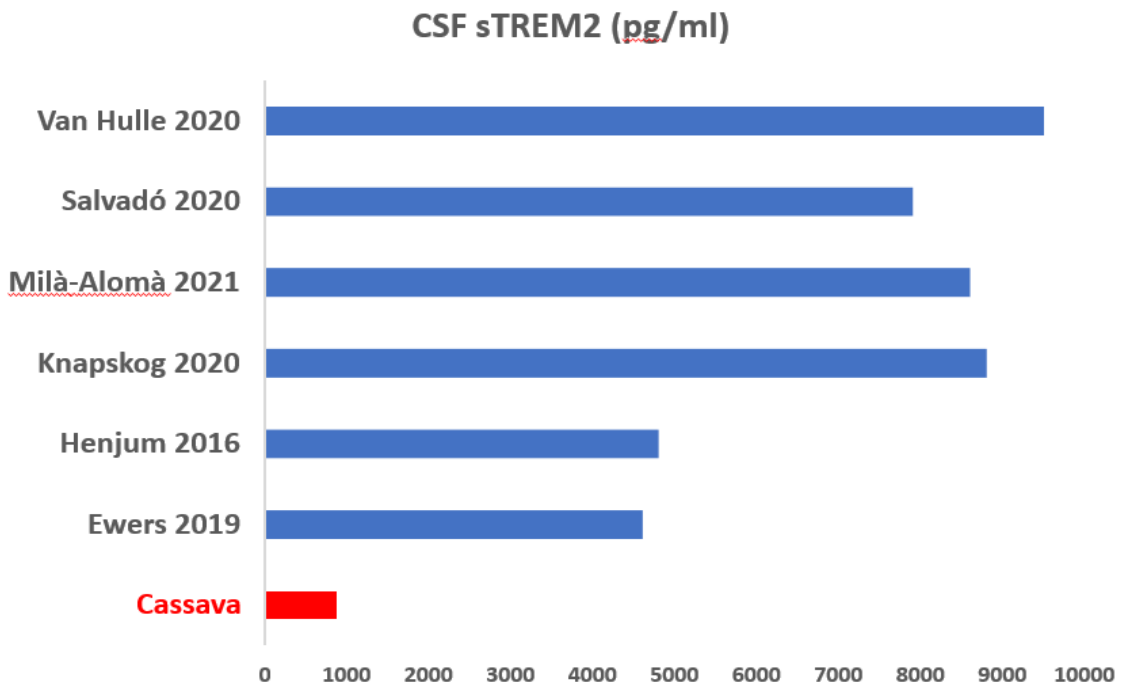
First is the CSF/plasma albumin ratio, which is a clinical lab test and is fairly uniform across individuals (even with AD) at 5-10. The following link from Allina Health (https://account.allinahealth.org/library/content/49/150212) advises elderly patients that they should expect a value of **8-9**. Dr. Wang measured **0.24**. Exemplary published studies of CSF/plasma albumin in AD are compared to Cassava's redo. All references will be provided upon request.



Another seemingly problematic assay concerns the baseline for IL-6, which is an inflammatory biomarker that is elevated in autoimmune diseases. In other AD studies, CSF IL-6 levels are **1-5** pg / mg. The baseline IL-6 averages Cassava reports for IL-6 in the redo are **33-34** pg / ml. Exemplary published studies of CSF IL-6 levels in AD patients are compared to Cassava's redo. All references will be provided upon request.



Furthermore, the sTREM2 baselines in the redo is far outside other published studies. Exemplary published studies of CSF sTREM2 in AD are compared to Cassava's redo. All references will be provided upon request.



5. Apparent False and/or Misstatements in Cassava's Phase 3 SPA Request

On August 24, 2021, Cassava Sciences announced "Agreement with the FDA on Special Protocol Assessments (SPA) for its Phase 3 Studies of Simufilam for the Treatment of Alzheimer's Disease." (https://www.cassavasciences.com/news-releases/news-release-details/cassava-sciences-announces-agreement-fda-special-protocol). According to current governing regulations, and good public policy, this approval should be rescinded.

In the FDA "Special Protocol Assessment—Guidance for Industry" book (https://www.fda.gov/media/97618/download) on Page 16, the agency states clearly and unequivocally that its approval can be rescinded if "[t]he relevant data, assumptions, or

information provided by the sponsor in the SPA submission are found to be false statements or misstatements".

Cassava's Phase 3 Special Protocol Assessment (SPA) for Simufilam was supported by preclinical studies and phase 2a and phase 2b biomarker studies. For the many reasons enumerated in my original Citizen's Petition and the two supplemental submissions, we strongly believe that countless such false and misleading statements have been made by Cassava Sciences. Whether these troubling statements by the company were made intentionally or not doesn't alter the need for the FDA to reevaluate the research underlying Simufilam and the agency's existing power to rescind its Phase 3 SPA approval.

The 2019 phase 2a data are largely Western blot experiments from Dr. Wang and some of these have been flagged by leading independent scientific integrity experts. According to the company's most recent public statement, the original data were apparently not maintained or retained by Cassava. The inconsistent phase 2b biomarker studies seem tainted by the fact that at least the redo was done by Dr. Wang and not by an "outside" lab as Cassava repeatedly claimed in public statements. Now, it seems that three of the ten biomarker measures in the redo are wholly inconsistent with expectations.

For the foregoing reasons, in addition to our original request that Cassava Sciences clinical trials be paused pending a thorough investigation and audit, I also respectfully recommend rescinding the recently announced SPA for Simufilam.