November 16, 2021

Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20857

VIA USPS

CITIZEN PETITION
This petition for administration 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") immediately expedite approval of the drug Simufilam pursuant 21 U.S. Code § 356 - Expedited Approval of drugs for serious or life-threatening diseases or conditions.

1. ACTION REQUESTED

Petitioner is requesting the FDA for Accelerated Approval of Simufilam for the most significant unmet medical need in the United States of America.

1. STATEMENT OF GROUNDS

Artist William Utermohlen was diagnosed with AD (Alzheimer's disease) in 1995. In the figure above, he painted what he saw in the mirror. As William Utermohlen's Alzheimers progressed, his understanding of the world rapidly declined. From his last painting in 2000, we see that he spent the final seven years of his life incapable of seeing the world, effectively blind. He passed away in 2007.

This view of AD from a patient perspective is tragic and touching. It elicits anxiety for those of us with sound minds. What is it like to look into the mirror, unable to see one's own face for seven years? What else are they unable to see?

I review these weighty problems with the FDA to help frame my logic and construct a petition for why Simufilam must be expediently granted accelerated approval and advanced to phase 4 post-marketing surveillance based on the risk-benefit analysis below.

After reviewing the FDA's mission statement, I am operating on the premise that the FDA evaluates medications based on **risk benefits**.

1. There is an overwhelming and urgent need ("**An Unmet Medical Need**")
2. Simufilam has consistently reported an excellent safety and tolerability profile. (**The risk**)
3. The cognitive data, by my judgment, is a treatment effect, not placebo. (**The benefit**).

(1) Overwhelming Public Need

I practice at one of the largest community hospitals in the southeast. As you know, AD patients are twice as likely to be admitted to the hospital as non-AD patients. AD is predictive of an extended and complex hospital stay with increased odds of death compared to patients who do not have AD. AD-associated hospital stays are 22% more likely to get readmitted within 30 days. The severity of the above statistics has remained stable from 2008 to 2020. **Twelve years of medical advancements have not benefited AD patients.** (https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf page 53).

I have witnessed numerous families bring their elderly father or mother to the ER, saying, "we cannot take care of him/her." Not because they are forgetful, but because they are easily agitated and turn aggressive. These families do not ask, "is there a treatment?". They have already navigated a complex medical system and know AD is terminal with **no effective treatment.** Heart attacks, strokes, sepsis, and other diseases seen in hospitals have a myriad of remedies. AD does not. AD is the sixth leading cause, and by some estimates, it is the third leading cause of death. See "[2021 ALZHEIMER'S DISEASE FACTS AND FIGURES](https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf)"

As a patient advocate, I elected to add anecdotal data (in addition to population statistics) to contextualize and humanize why AD is the greatest unmet medical need.

(2) Safety Data

Simufilam has been administered to patients across five trials (ClinicalTrials.gov Identifier: NCT03748706, NCT04079803, NCT04932655, NCT04388254, NCT04388254).

More precisely, 39,620 doses of Simufilam were administered from the publicly available data, with no reported serious *adverse* events. Further, Patients tolerated Simufilam well, as is evident by the low attrition rate (less than 10%).

In addition, there are 150 patients enrolled in the "open-label extension trial" (OLE). They do not have publicly available information; however, it is reasonable to assume the FDA is privy to safety data. The standard protocol requires study sites to report serious adverse events immediately to the FDA. Those OLE patients were administered another 109,500 doses.

Factoring in the OLE patients, in totality, **149,120 doses** were administered without serious safety events across multiple trials. **Simufilam is safe and well-tolerated.**

(3) The data:

Data associated with Simufilam has been remarkably consistent across different trial sites and over time.

A 28 day multi-center, placebo-controlled, randomized trial with 64 patients measured:

1. Abeta42
2. Total Tau
3. P-tau181
4. Neurogranin
5. Neurofilament Light Chain
6. YKL-40
7. Paired Associates Learning Test
8. Spatial Working Memory Test
9. IL-6
10. sTREM2
11. HMGB1
12. Albumin
13. IgG
14. Filamin A Linkages to alpha7 Nicotinic Acetylcholine Receptor
15. Toll-like Receptor 4 in Subject Lymphocytes
16. Plasma P-tau181
17. SavaDx

Cassava Sciences stated:

"98% of patients treated with Sumifilam 50 mg or 100 mg b.i.d. for 28 days showed improvements in validated biomarkers of AD pathology; neuroinflammation; and neurodegeneration; with no safety issues."

Open-label Extension data tested:

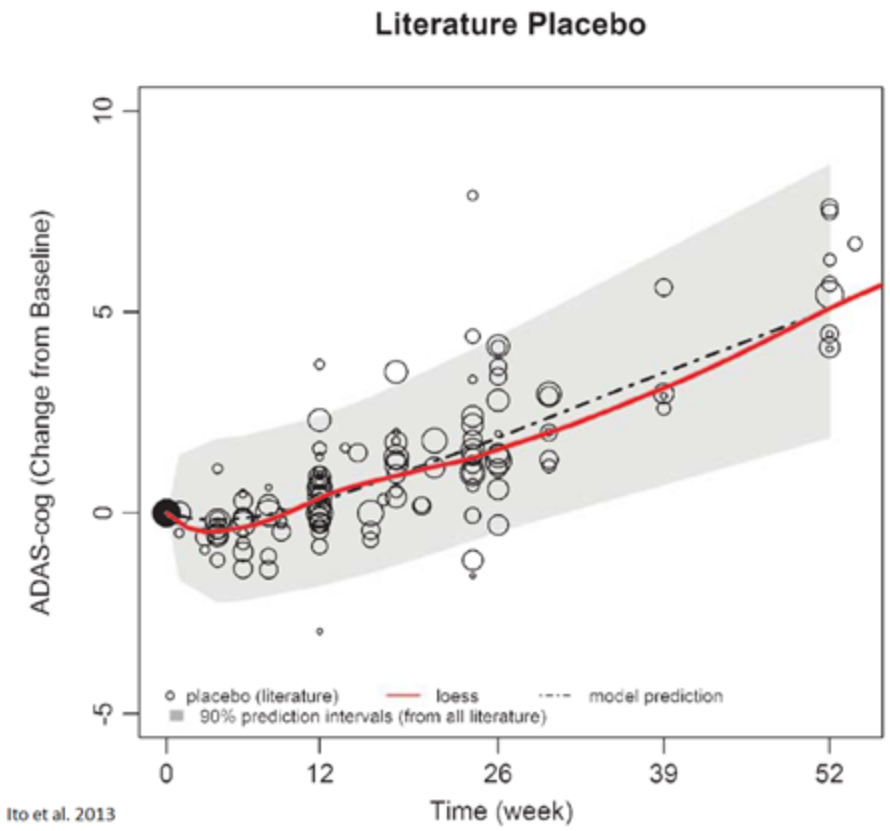
1. P-tau
2. Total Tau
3. Abeta42

4. Neurofilament light chain
5. Neurogranin
6. YKL-40
7. Soluble TREM2
8. HMGB1
9. ADAS cog-11 (reported at 6, 9, and 12 months)
10. NPI (reported at 6, 9, and 12 months)
11. SavaDx

Tallied up, we have 34 different measures over twelve months and twenty-eight days. The biomarker results are groundbreaking for an AD drug. Unlike previous AD drugs that directly target the biomarker (and thus only affect that one biomarker), simufilam affects *all* essential biomarkers. This increases the chances of success as Aβ42/40 ratio and ptau181 correlate directly with Alzheimer's disease progression. The worse you are clinical, the worse these markers are. Whereas Biogen's Aduhelm decreased pTau-181 levels by 13-16% at 12 months, Simufilam at 6 months already decreased it by 18%.

Now, let us focus on the data which is clinically the most relevant-ADAS-Cog, and NPI.

A valid criticism of the twelve-month OLE data is that it is open-label, susceptible to placebo effect. However, a more comprehensive look into the literature concerning AD, ADAS-Cog, and placebo reveals the treatment effect is highly probable and placebo effect unlikely.



A meta-analysis (https://alz-journals.onlinelibrary.wiley.com/doi/10.1016/j.jalz.2009.05.665) published by Ito et al. looked at placebo response data in 19,972 patients between 1990 and 2008. The disease progression in mild to moderate AD patients was estimated at 5.5 points per year.

The disease progression model proposed by Ito et al. shows the expected cognitive decline over time within a 90% prediction interval (shaded area). This suggests a limit to the observed placebo effect as patients do not typically improve from baseline past six months. In a follow-up analysis (https://pubmed.ncbi.nlm.nih.gov/23803296/), Ito et al. also highlight that the placebo response tends to be more significant in the first few months.

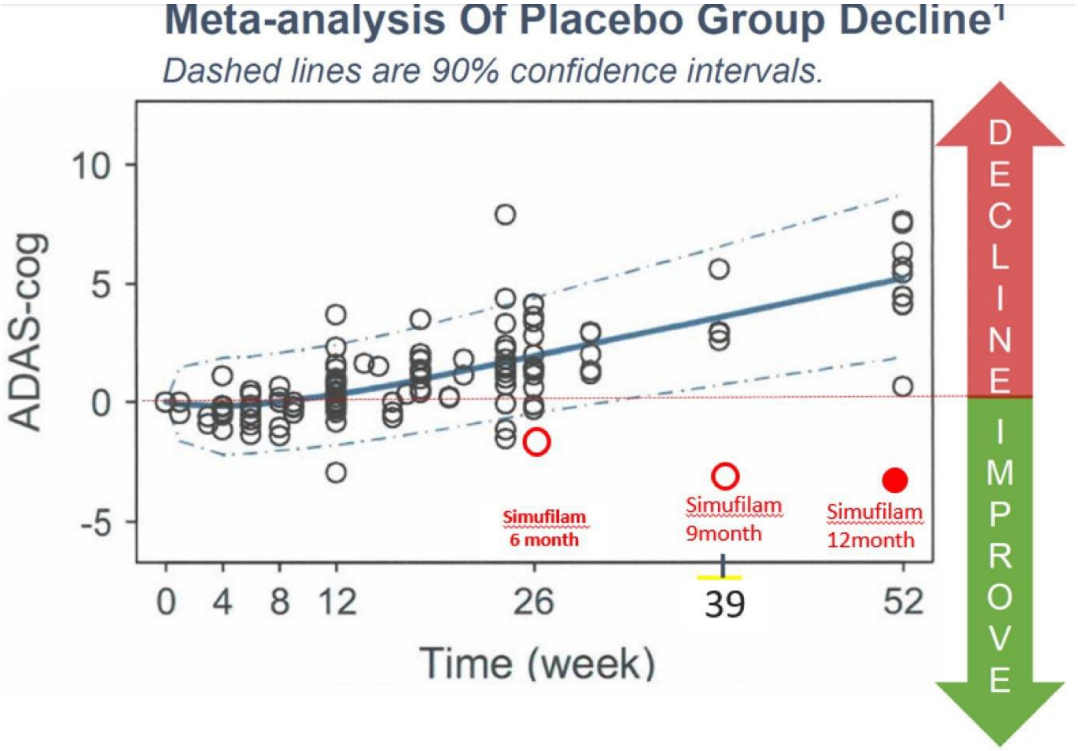
Table 4 Subgroup analysis of disease progression rate

	Uncorrected disease progression rate, points/year, mean (95% CI)	Covariate-corrected disease progression rate, points/year, mean (95% CI)	Maximum extent of placebo effect, points mean (95% CI)
Overall	5.77 (5.60, 5.94)	5.86 (5.75, 5.97)	− 1.89 (− 2.08, − 1.69)
Publication year			
< 2008	6.13 (5.89, 6.39)	5.92 (5.80, 6.04)	− 1.70 (− 2.04, − 1.36)
≥ 2008	5.56 (5.40, 5.73)	5.81 (5.72, 5.92)	− 2.03 (− 2.24, − 1.81)
Trial design			
Add-on	5.53 (5.26, 5.80)	5.85 (5.69, 6.00)	− 1.92 (− 2.25, − 1.59)
Non-add-on	5.84 (5.64, 6.04)	5.87 (5.74, 6.01)	− 1.88 (− 2.11, − 1.65)
Regions			
International	5.81 (5.66, 5.97)	5.78 (5.67, 5.90)	− 2.17 (− 2.39, − 1.95)
North America	5.62 (5.35, 5.89)	6.11 (6.00, 6.23)	− 1.50 (− 1.69, − 1.31)
Europe/Oceania	5.58 (4.68, 6.48)	5.54 (4.79, 6.29)	− 2.35 (− 3.80, − 0.90)
East Asia	5.67 (5.15, 6.19)	5.45 (4.93, 5.97)	− 2.43 (− 3.45, − 1.41)
Middle Asia	7.00 (5.98, 8.02)	6.76 (6.20, 7.31)	− 0.01 (− 1.31, 1.28)
South America	7.27 (6.49, 8.06)	6.27 (5.48, 7.06)	− 1.35 (− 2.11, − 0.60)

The values have been converted to annual disease progression rate, *a* (points/week) × 52 weeks/year

A follow-up meta-analysis by [Zhang et al](https://alzres.biomedcentral.com/articles/10.1186/s13195-020-00630-5). also looked at placebo response data in 19,210 patients between 1992 and 2019. The disease progression rate was estimated at 5.82 points per year. It's also suggested that placebo effect plateaus at approximately 16 weeks in clinical trials.

Simufilam's ADAS-cog data superimposed on Cohorts mentioned above:



The data from Ito et al. and Zhang et al. all conclude that the placebo effect has its limits. A similar pattern can be seen by evaluating the placebo group of Aduhelm. Placebo's effect is less robust and shorter-term. Based on the three sizable cohorts, clear cognitive decline is expected and undeniable as measured by ADAS-Cog. Further, it is predictable and measurable. Across the two metal analyses and Aduhelm trial the ADAS-Cog declined from 5.2 to 5.8 point decline. If a treatment group can show a large enough benefit, such as an improvement from baseline ADAS-Cog at twelve months or greater. In that case this is likely beyond the extent of the observed placebo effect in published literature. We will discuss the significant treatment effect noted below.

Taking a closer look at the delta between the placebo cohorts (discussed above) and the OLE ADAS-Cog data, overall, the delta is an astonishing 8.2-9.2. In addition, subgroup analysis shows 68% of the patients had an improvement of ADAS-Cog of 6.8. This cohort's delta is 11.8 to 12.6. A placebo effect can not explain this, in my estimation.

Suppose the FDA is looking for a twenty percent decline in the rate of the natural progression of AD, then that is equivalent to ADAS-cog 4.64 - 4.16. and respective deltas of 1.16 -1.04 based on the 40,000+ placebo cohort. Effectively Simufilam would have to perform at 14% of its OLE data to get approval based on FDA's treatment of Aduhelm, Donanemab, Gantenerumab. The three mentioned AD medications had received AA or BTD based on inferior clinical response to Simufilam. This, plus considering the supportive surrogate data, makes Phase 3 a foregone conclusion.

Lets review trials with already approved AD medications from open label data. Does open-label status make the data look more positive than it should be? This study (Safety and Efficacy of Donepezil HCl 23 mg in Patients With Moderate to Severe Alzheimer's Disease - Study Results) and this study (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2034585) of existing AD drug donepezil was open-label. Yet, patients declined after six months, which is not significantly different from the randomized control data. This implies that when it comes to AD, an open-label and a controlled study gives similar results.

Study Timeline	NPI Scale
Baseline	No neuropsychiatric symptoms in 34% of patients
6 months	No neuropsychiatric symptoms in 38% of patients
9 months	No neuropsychiatric symptoms in >50% of patients

As mentioned above, behavioral disturbances are the primary reason families abandon their loved ones in the ER. Caregiver stress is cited in "Alzheimer's facts and figures" as having numerous unfavorable outcomes. Worse, physicians are often forced to use antipsychotics for dementia-related psychosis and agitation, which increases the risk of death in the elderly. Physical restraints are an unfortunate last resort used in the hospital setting to prevent patients from harming themselves and staff.

Psychotic symptoms have been correlated with increased neurofibrillary tangles (https://pubmed.ncbi.nlm.nih.gov/11115331/) and increased levels of hyperphosphorylated tau.

(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4034758/). Simufilam has shown it can decrease Total tau and Phospho-tau (pT181) in three separate biomarker studies.

The incidence of at least one NPI symptom in AD and dementia is high, although prevalence rates can vary widely. A summary of the observed prevalence of NPI symptoms in published literature is listed below:

75% of dementia participants exhibited at least 1 NPI symptom
(https://pubmed.ncbi.nlm.nih.gov/12243634/)

88% percent of AD patients exhibited at least 1 NPI symptom
(https://pubmed.ncbi.nlm.nih.gov/8559361/)

92% of patients had at least one dementia-related behavior
(https://pubmed.ncbi.nlm.nih.gov/15271114/)

Behavioral disturbances occurred in 98% of AD patients
(https://pubmed.ncbi.nlm.nih.gov/10804073/)

Neuropsychiatric symptoms were prevalent across all clinical AD stages: ≥1 NPS 81.4% in SCD, 81.2% in MCI, 88.7% in dementia
(https://n.neurology.org/content/97/13/e1276)

Simufilam use resulted in markedly fewer behavior disturbances, and this data continues to improve with time.

Fast-tracking a medication after a single-arm study (open-label data) is not unprecedented. The FDA, as Ke Liu, MD, PhD cites
[here.](https://www.ema.europa.eu/en/documents/presentation/presentation-us-fda-expedited-programs-expanded-access-ke-liu_en.pdf), has taken this action when there is an unmet medical need.

As is known, the cognitive data was collected over sixteen clinical sites across the US and Canada by independent physician principal investigators and associated staff (unaffiliated with Cassava Sciences). These sites also perform trials for AD drugs by Biogen and Eli Lilly. Additionally, the chain of custody was made transparent and verified by two independent biostatisticians.

AD claims the lives of 13 patients every hour. If the FDA allows phase three trials to continue for two years, then we risk the deaths of over 240,000 patients.

Functional status is an excellent predictor of morbidity and mortality. I believe by preserving cognitive function, Simufilam will also preserve functional status (as the two are highly correlated). It may take years to see a mortality benefit, but waiting years in the setting of limited risk is unacceptable, in my humble opinion.

1. ENVIRONMENTAL IMPACT

Petitioner states that the approval 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.

1. ECONOMIC IMPACT

Alzheimer's Disease affects over 6 million people in the United States. It is the fifth leading cause of death in seniors. The total healthcare costs in 2020 is estimated to be $305 billion according to the NIH (https://pubmed.ncbi.nlm.nih.gov/32840331) and soon to grow to $1

trillion as our population ages. Even this figure does not take into account the indirect costs including informal care by family caregivers, societal and personal burden of the disease. Successful treatment may delay the progression of Alzheimer's disease, thereby easing the burden on nursing homes and hospice services.

1. CERTIFICATION

The undersigned certifies that this petition includes all the information and views on which the petition relies and that it includes representative data known to the Petitioner that may be unfavorable to this petition. I am optimistically submitting this Citizens Petition to review my risk-benefit analysis. Simufilam is safe, effective, and required urgently for an unmet medical need. I look forward to the FDA's correspondence.

Respectfully submitted,

Imran Khan, MD
Associate Professor of Internal Medicine