Simufilam as a Savior or a Simple Illusion?

A Detailed Analysis of SAVA and its lead drug candidate: Simufilam.

A Paper Presenting Why We Are Convinced that SAVA is a Short.

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Disclaimer

The authors of this paper have a financial interest in the stock SAVA – as a decline in the price of the stock would result in financial gains for the authors. The investment of the authors is of a bearish nature in relation to SAVA's lead drug candidate – Simufilam. The authors expect the clinical results of the Phase III trial of Simufilam to be deceiving, leading to a sharp decline in the stock price of SAVA – from which the authors would profit financially.

This paper is solely based on the authors' readings and analysis of the data that will be presented in this paper. No investment decision should be made solely based on the reading of this paper. This paper does not constitute any type of financial advice and is only there to present the authors' analysis and personal opinions on SAVA.

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Executive Summary

Cassava Sciences (SAVA), a clinical-stage biotechnology company focused on Alzheimer's disease (AD), has gained substantial attention due to its lead drug candidate, Simufilam. Positioned as a novel treatment, Simufilam targets filamin A (FLNA), a protein that, according to the company, plays a key role in neurodegeneration and inflammation in AD. This innovative mechanism has been promoted as a potential breakthrough in AD treatment, distinguishing it from traditional approaches that focus on amyloid plaques and tau phosphorylation.

Despite the market's enthusiasm and the company's optimistic portrayal, significant concerns persist within the scientific community about the coherence of Simufilam's mechanism of action (MOA). Skeptics argue that the underlying FLNA hypothesis lacks sufficient independent validation and that the drug's ability to impact the complex pathology of AD is still not proved. These scientific doubts are compounded by controversies surrounding Cassava Sciences' research practices. Including the scrutiny from regulatory agencies over data integrity, which further undermines confidence in the company's claims.

This paper provides a thorough analysis of the scientific foundation of Simufilam, detailing the fundamental flaws in its proposed MOA. We also examine the company's clinical trial structure, which may exacerbate existing issues in its Phase III trials. Given the high probability of failure in these trials, we outline the financial ramifications for Cassava Sciences and present a strong case

for our short position. We are anticipating a sharp decline in the stock price - considering that the company's sole product will most probably fail its Phase III clinical trials.

Our assessment assigns a probability of success (POS) for Simufilam in its Phase III trial to be between 0.00032*% to 0.0034%* chance of success, indicating a high statistical likelihood of failure. While these numbers may support a strategy of shorting the stock, it's important to acknowledge the inherent unpredictability in drug development, which can sometimes defy statistical odds.

Currently, Cassava Sciences is valued at a market cap of *$1.39 billion,* a figure heavily contingent upon the prospective success of Simufilam. As we anticipate an inevitable failure of the Phase III trials - expected for Q4 2024.

Post-failure, we project that Cassava Science' stock will adjust to trade at or near its cash reserves. According to their *Q2 2024 10-Q filing,* the company reported *$207.3 million* in cash. However, factoring in the *$40 million* settlement with the SEC, we estimate their current cash position to be approximately *$167.3 million*. Additionally, in their *last press release*, Cassava Sciences projected a net cash use of *$80 to $90 million* for the second half of 2024, including the *$40 million* settlement. This would leave them with an estimated cash balance between *$117 and $127 million* by year-end.

Consequently, when computing the anticipated collapse, the company's valuation is likely to be restricted to its cash holdings, if not less, due to the inevitable mass sell-off. Based on these considerations, we predict that the share price will drop from *$28.98* to a range approximately *$3.49 to $1.94* - reflecting the market's recalibration to the company's cash value in the aftermath of Simufilam's failure.

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The Intersection of Risk, Knowledge, and Uncertainty in Biotech Shorting

Short selling is more than just a financial strategy, it is a complex engagement that involves risk, uncertainty, and the limits of human knowledge. Unlike traditional investments - where one assumes a company's growth and success - shorting relies on failure. This entails an intricate interplay between what is known, what is speculated, and what is inherently uncertain. When applied to a biotechnology company - where success or failure hinges on the unpredictable results of scientific trials - the act of shorting a company becomes even more complex. The unknowns are magnified by the complex and volatile nature of drug development - where scientific discovery intersects with market speculation. The rational investor must carefully navigate these murky waters, balancing risk and reward while confronting the fundamental limitations of human knowledge.

In this paper, we explore the rationale behind shorting Cassava Sciences based on the predicted failure of its Phase III clinical trials. Our approach will be grounded in a careful analysis of the scientific and non-scientific factors at play, but first, we must acknowledge the deeper questions that underpin such a decision. These include how we come to know what we know, how we assess risk, and how we cope with uncertainty when engaging with the unknown. By exploring these questions, we aim to set the tone for a rigorous analysis that not only explains why we believe that the *Rethink.Alz's* trial is highly probable to fail.

What Do I Know, and How Do I Know it?

At the center of any decision to short a stock lies the question of knowledge. How do we know that a company's drug will most probably fail its clinical trial? More specifically, what kind of evidence do we rely on to make such a prediction, and how confident can we be in the reliability of this evidence?

Shorting is, in many ways, an epistemological exercise. The investor is betting that his knowledge about the future - based on the interpretation of data, trends, and probabilities - is more accurate

than the market's current assessment. However, in a field like biotechnology, where uncertainty is pervasive, the limits of what we can know are profound. Drug development is a complex process, and even the well-informed experts often struggle to predict the outcomes of clinical trials. In making the decision to short a biotechnology company, it is essential to ask whether the prediction of failure is based on solid evidence or mere speculation. Scientific data, trial results, historical trends, and experts' opinions all contribute to forming a well-reasoned prediction – acknowledging that each piece of evidence carries varying degrees of reliability.

- **Known Factors**: Known factors are the concrete, verifiable data points that can inform a rational decision. These include the results of earlier clinical trials (Phase I and Phase II), the company's history, the strength of its scientific approach, and the expertise of its research team. If the Phase II trial showed lackluster efficacy or raised safety concerns, these are clear indicators that the Phase III trial might face significant hurdles.

- **Unknown Factors**: However, the unknowns are just as important to consider. What are the limits of your knowledge? Are there variables in the trial design, patient population, or regulatory process that could affect the outcome in ways you cannot foresee? In biotechnology, unpredictable biological responses, regulatory shifts, or even patient recruitment issues can all change the course of a trial. These unknown factors represent a major risk, and an investor must acknowledge the inherent limits of what can be known.

How To Evaluate Scientific Risk?

Risk evaluation in science, particularly in drug development, is inherently associated with uncertainty. Clinical trials are probabilistic by nature - success is never guaranteed, and failure is often more likely than success. Predicting a decline in the stock's price based on a clinical trial's expected failure is to engage directly with this risk, attempting to quantify and predict it - based on available data. But how does one evaluate this risk with any degree of certainty?

Shorting is not merely a question of whether a stock will decline; it involves an understanding of the specific risks associated with predicting a failure. These risks are both statistical and market driven. Any rational investor must carefully weigh them before making a decision.

- **Statistical Uncertainty**: Clinical trials, especially in Phase III, are inherently unpredictable. Even if earlier trials showed mixed or negative results, a chance remains - however slim - that the drug could succeed. Statistical uncertainty comes into play when considering how likely it is for the drug to clear its efficacy and safety benchmarks. For example, the FDA might approve a drug that shows only marginal improvement over existing treatments, or the company might adjust trial endpoints in a way that favors approval. How do you assess this statistical uncertainty, and what probability do you assign to the trial's success versus failure?

- **Market Risk**: In addition to statistical uncertainty, there is the risk that even if the trial fails, market dynamics might prevent the stock from falling as expected. Biotechnology stocks are notoriously volatile, and investor's sentiment can swing dramatically in response to news even if the underlying scientific results remain unchanged. What if the company announces a partnership, secures additional funding, or pivots to a different strategy after a trial failure? These are all risks that could undermine the expected rewards of a short position.

How Confident Can I Be in My Knowledge and Reasoning?

After evaluating the evidence and risks, the next question is one of confidence. How sure are you that your prediction is correct? In epistemology, the concept of *epistemic justification* refers to the degree to which a belief is supported by evidence and reasoning. Shorting a stock is a high-risk proposition, and thus requires a high degree of epistemic justification.

Confidence in an investment decision must stem from a well-rounded understanding of both the evidence and the risks. It requires rigorous due diligence and a willingness to confront the limits of your knowledge. Have you thoroughly analyzed the scientific literature? Do you understand the drug's mechanism of action, the trial's design, and the regulatory landscape? If so, you may feel justified in your decision to short a stock. However, even with thorough research, confidence

should be tempered by the recognition that uncertainty is an inherent part of both science and investing.

What Am I Not Seeing?

One of the most dangerous traps in investing is the failure to account for hidden risks. These are the factors that you might not initially consider but could dramatically affect the outcome of your short position. Identifying hidden risks requires a combination of both skepticism and foresight. As well as the humility to acknowledge that no prediction can be entirely foolproof.

Hidden risks in biotechnology might include unexpected regulatory decisions, off-label drug use, or even public relations campaigns that shift investors' sentiment. Moreover, there is always the possibility of unforeseen scientific developments - such as new data that suddenly changes the landscape of the clinical trial. While shorting assumes that failure is likely, hidden risks remind us that the future cannot be known. Does the company have a contingency plan that you haven't considered? Is there a possibility that a competitor's failure could suddenly make this company's drug more valuable? These are just some of the hidden risks that must be accounted for.

How Do I Know for Sure?

Skepticism, the philosophical stance that questions the possibility of certainty, plays an essential role in any serious investment decision. While shorting is often seen as a bold move, it should be grounded in a deep understanding of the inherent uncertainty of the future. No matter how well-reasoned a prediction may be, it is crucial to ask: how can we know this for sure?

- **Due Diligence**: To mitigate the uncertainty, due diligence is key. This includes not only analyzing the available data but actively seeking out alternative perspectives. Have you consulted experts in the field? Have you explored the possibility that your interpretation of the data is flawed or incomplete? Rigorous due diligence is not just about gathering information, it's about challenging your assumptions and actively looking for counterarguments.

- **Probability, Not Certainty**: The goal is not to achieve certainty - this is impossible, as anything is possible - especially in a field as interconnected and complex as the life sciences. Instead, the goal is to make the most informed, rational decision based on the probabilities. A Phase III trial has inherent risks, but the question is whether the probability of failure is high enough to justify the risk of shorting the stock. The investor must balance the evidence and ask, probabilistically, whether the expected outcome justifies his position.

Could My Assumptions Be Wrong?

Fallibilism, the philosophical principle that acknowledges the possibility of error in all human beliefs, is critical in investment decisions. Even the most well-researched, well-reasoned predictions can be wrong. Recognizing this fact is not a sign of weakness but of intellectual maturity and preparedness.

In any short position, it is vital to confront the possibility that your assumptions could be flawed. Have you made sure to consider alternative viewpoints? Have you actively sought counterevidence that might weaken your thesis? Fallibilism encourages investors to remain open to new information and to be willing to change course if the evidence shifts. This means that one must remain vigilant about any new developments that could affect the outcome of the trial or the stock's performance.

- **Seeking Counterevidence**: A key part of this process is actively seeking counterevidence. This might involve reading analyses that take a more optimistic view of the drug's chances, or consulting experts who believe the trial could succeed. By engaging with opposing views, you can refine your thesis and ensure that your assumptions are as robust as possible.

Key Takeaways

Shorting a biotechnology company's stock based on the anticipated failure of its Phase III clinical trial is a high-risk, high-reward strategy that demands careful reflection. At its core, this decision involves engaging with the unknown - evaluating scientific risk - confronting the limits of knowledge and weighing uncertainty. By asking critical questions about what we know, how we

evaluate risk, and how confident we are in our predictions, we can approach shorting with a greater sense of intellectual rigor and preparedness.

In the pages that follow, we will build on this foundation by delving into the scientific rationale behind our prediction that Cassava Sciences' Phase III trials for Simufilam are most probable to fail. Through a careful examination of the data, trial design, and market conditions, we aim to provide a reasoned justification for our view - all while keeping in mind the broader uncertainties that define the world of biotechnology investment.

Key Reasons Why We Are Shorting Cassava Sciences:

- **Scientific facts contradict the company's claims.**
  Physiochemistry properties, protein-protein interactions, and other critical factors indicate that Simufilam's efficacy is unlikely.

- **Simufilam's mechanism of action lacks robust scientific support.**
  The drug's purported action on FLNA to restore the function of nicotinic acetylcholine receptors (nAChRs) and reduce toxic amyloid-beta (Aβ) oligomer signaling is theoretically appealing but lacks validation in independent peer-reviewed studies.

- **The central hypothesis is speculative and controversial.**
  Cassava Sciences' central theory that modulating FLNA can significantly alter the course of AD is not grounded in well-established AD pathophysiology. This unproven hypothesis forms the basis for Simufilam; however, without substantial support from broader scientific research, it remains highly questionable

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- **Clinical trial results have been insufficient, inconsistent, and plagued by methodological concerns.**

  The clinical trials conducted thus far regarding Simufilam have been marked by methodological issues and concerns about data integrity.

- **Alzheimer's disease drug development has a high failure rate.**

  With over 98% of AD drug candidates failing in clinical trials over the past decades. Simufilam shows no exceptional data that suggests it will break this trend. The drug's unproven mechanism and its questionable clinical and preclinical results regarding the SEC's report are to be factored in when computing its prospects.

- **Cassava Sciences' market valuation is inflated by speculative science.**

  Investor enthusiasm for Simufilam is based on a speculative and unverified scientific premise, leading to an overvaluation of Cassava's stock.

Overview of Cassava Sciences and Simufilam

Cassava Sciences was founded in 1998 under the name *Pain Therapeutics*, initially focused on pain management treatments. However, after a series of failures, including multiple FDA rejections of its painkiller products Remoxy (Terry, 2018), the company shifted its focus to neurodegenerative diseases, particularly AD, in 2017 (Terry, 2018).

Simufilam, Cassava Sciences' flagship product for AD, shares the same target established by Dr. Hoau-Yan Wang for Naloxone (VAKGL). Simufilam and Naloxone both have a similar – if not identical – target, the scaffolding protein FLNA. Cassava Sciences now claims that misfolded FLNA contributes to Alzheimer's pathology.

In 2019, to reflect this shift in focus the company rebranded as *Cassava Sciences*. Simufilam is now positioned as a novel treatment for AD (*PTIE 8-K 20190327*, 2019).

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Simufilam's Proposed Mechanism of Action

Cassava Sciences claims that Simufilam works by targeting FLNA, a scaffolding protein that plays a role in various cellular processes, including the regulation of the cytoskeleton and cell signaling. According to Cassava Sciences - in AD - FLNA becomes misfolded causing a disruption of its normal role and contributing to pathological signaling (Cassava Sciences, 2024). Specifically, Cassava Sciences posits that misfolded FLNA enhances the interaction between Amyloid beta (Aβ) oligomers and the α7 nicotinic acetylcholine receptor (nAChR), thereby amplifying the neurotoxic effects of Aβ (CTAD 2023 Poster Presentation). Simufilam is supposed to restore the normal structure of FLNA, reduce pathological signaling via nAChRs, and improve cognitive function. Cassava also claims that Simufilam suppress overactive mammalian target of rapamycin (mTOR) (Press Release, 2023), (Wang et al., 2023).

This mechanism seems appealing because it provides an alternative approach to targeting Aβ directly, focusing instead on a downstream modulator of Aβ toxicity. However, there are several key issues with this hypothesis and the proposed action of Simufilam that warrant a closer examination.

Scientific Factors Proving Simufilam Will Most Likely Fail

Several critical scientific factors undermine Simufilam's proposed mechanism and suggest that it is highly improbable that it will be an effective treatment for AD.

1. LogP value
2. Potential problem of potency.

3. Protein to protein interaction.
4. Naloxone binding to FLNA (VAKGL peptide in FLNA).
5. FLNA discords, use in AD and
6. Hyperphosphorylation- Not a kinase
7. Alpha 7 already used and failed in AD both inhibited and activated.
8. AB42 toxicity is from too many causes – Lack of Direct Amyloid Clearance and no tau solution.
9. Dimebone Phase III fail

1. LogP Value and Drug Bioavailability

The octanol-water partition coefficient (logP) value of a drug is a key determinant of its bioavailability, particularly in crossing the blood-brain barrier (BBB). For an AD drug to be effective, it must efficiently penetrate the brain. Simufilam's LogP value - the balance of its hydrophilic and lipophilic properties - determines whether the drug can adequately reach its target in the brain. If the LogP is too low, it won't cross the BBB, and if too high, it may accumulate in fatty tissues, leading to toxicity or poor brain penetration.

Looking at Simufilam's properties one thing can directly strike us, its LogP and half-life values. Both values are critical in the impact and influence of a drug and are lacking for Simufilam. With a reported LogP value of 1.1 and a half-life of 4.5 hours (PubChem) (Alzheimer's Drug Discovery Foundation).

Focusing on the LogP value, and its Importance in Neurodegenerative Diseases such as AD

The LogP is an important physiochemical parameter that takes account of a drug's hydrophobicity, and how the drug distributes herself in both an aqueous and lipophilic environment (Ditzinger et al., 2018). This provides a view of the drug's performance and reaction in the following behaviors: membrane permeability, absorption, solubility, distribution, binding, excretion, and CNS penetration.

In this instance, for Simufilam we mostly need to focus on the following behaviors: blood-brain barrier penetration (BBB), absorption, distribution to the brain, lipophilicity levels, and metabolic stability. Generally, for an oral drug that is aimed to treat neurodegenerative diseases, a LogP between 2 and 3 is considered optimal (Green, 2024) (Durrant Lab).

Furthermore, with this low LogP value, Simufilam could have multiple problems, such as poor BBB penetration. Indeed, with a value of 1.1, this indicates that Simufilam is relatively water-soluble. While this may help with dissolution in the gastrointestinal tract, it is certainly not advantageous when crossing the BBB, as it may encounter difficulties, as this membrane is rich in lipids. (*Current Opinion in Molecular Therapeutics*, 7(4), 408-413).

Simufilam needs to enter the CNS; its low LogP value indicates that it is prone to having issues crossing this membrane smoothly and attaining the primary site of the disease. As a hydrophilic drug, Simufilam will be at advantage when dissolving in the digestive tract, as stated previously, however it could have clear issues with its absorption through the intestinal lining into the bloodstream. This is because lipid membranes, such as those in intestinal cells, act as barriers to absorption (Hayton, 1980), and Simufilam lacks the lipophilicity needed to cross the lipid membranes efficiently.

Poor absorption in the bloodstream could have an impact on the bioavailability (Price et al., 2023), meaning that Simufilam would have a low level of success when reaching the CNS; therefore, a higher dose of Simufilam would be required to achieve the desired effects. When Simufilam arrives at the CNS, it will encounter another issue due to its low LogP: its distribution to the brain. Its hydrophilicity makes it less likely to effectively distribute itself to lipid-rich tissues, such as the brain (Dwibhashyam et al., 2008). This limited level of distribution could result in a limited, if not nonexistent, impact of Simufilam on AD. For this to be addressed, Simufilam would need much higher doses, which would automatically increase the risk of systemic side effects outside the brain. (Coleman et al., 2016). If Simufilam is not able to reach a sufficient level of concentration in the CNS then, its ability to treat Alzheimer's would be severely limited if non-existent.

Circling back to the half-life value of 4.5 hours that Simufilam has, its hydrophilic nature makes it prone to quick elimination via the kidneys (Garza et al., 2023). This necessitates a recurrent dosing for Simufilam to remain impactful - if it is. This rapid clearance might reduce Simufilam's efficacy over time.

Computation and Assessment of a pKa Value for Simufilam

Still, when assessing the LogP of Simufilam and therefore its BBB penetration, it is important to not only consider the LogP value in this evaluation. As assessing the pKa value is also a great indicator to evaluate the BBB penetration (Fong, 2016). Unfortunately, no pKa value is given for Simufilam on the website *PubChem.* A computation of Simufilam's approximate pKa value is still possible by simply looking at its chemical formula, 4-benzyl-8-methyl-1,4,8-triazaspiro (4.5) decan-3-one, and structure; see *Figure 1*. The amines, nitrogen atoms, have an averagely high pKa from 8 to 10 (Ashenhurst, 2023). The reason for this is that nitrogen atoms are easily protonated due to their basicity level (Lõkov et al.).

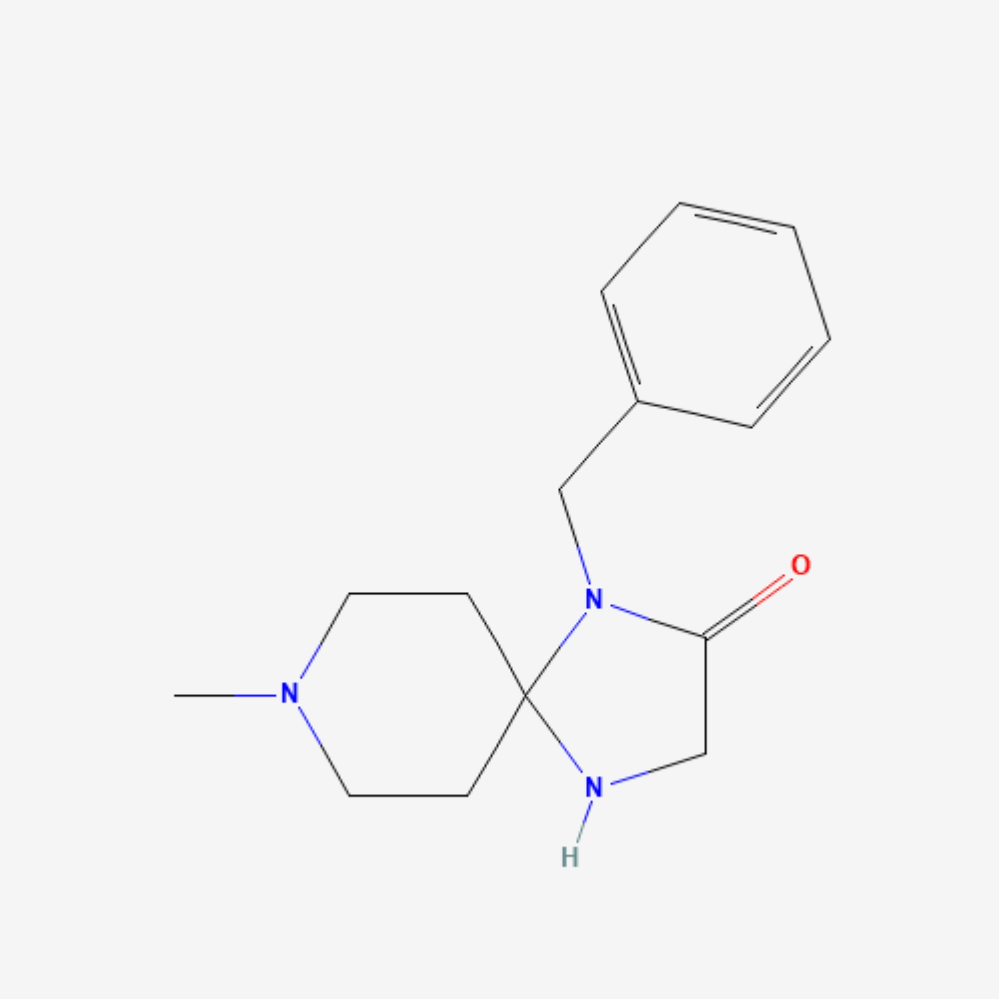

Figure 1. Chemical Structure Depiction of Simufilam (PubChem).

However, when evaluating Simufilam, the nitrogen atoms are included in a rigid spirocyclic system adjacent to a carbonyl group; this leads to an electron withdrawal by the carbonyl group (Contreras et al., 2005). The carbonyl group pulls electron density away from the nitrogen atoms that are close to it. This activity ultimately results in a reduction of the nitrogen atoms' basicity and, therefore, their pKa. Thus, a rough estimation can be made for the overall value of Simufilam's pKa value.

Considering the electron withdrawal mechanism that occurs via the carbonyl group from the nitrogen atoms, and the constrained spirocyclic ring of the nitrogen atoms. The pKa value is likely

to range between *6* and *7*, and not *8* to *10* as some might argue. The reason is that this estimation considers the reaction of nitrogen atoms in this type of environment: the CNS (Paulson, 1977).

The structural environment of Simufilam's nitrogen atoms, where steric hindrance and electron withdrawal effects lead to lower basicity. For an efficient BBB penetration, Simufilam should be non-ionized at physiological pH *~7.4* that would guarantee a maintained level of lipophilicity (Le, 2022). With its estimated pKa value being around *6* or *7*, the nitrogen atoms would be partially ionized with a pH value of *7.4*. However, Simufilam's lipophilicity would still be supplemented by the benzyl and methyl groups that compose it.

Their properties, along with Simufilam's size of *~259* g/mol, should, in part, compensate for the partial ionization and therefore allow Simufilam to achieve somewhat efficient BBB penetration. Nonetheless, this is all theoretical, and only reliable clinical or preclinical data should be trusted regarding the BBB penetration efficiency of Simufilam.

2. Potential Problems with Potency

Continually, another great indicator for a drug's success is its potency. When looking at the LogP value, we can hypothesize that its suspected poor bioavailability and poor brain penetration may indicate a clear struggle deficiency to reach an effective concentration at the target site in the CNS (Durrant Lab) (Pajouhesh et al., 2005). This would indicate a low level of potency for Simufilam, which may not deliver a sufficient level of active compound to the CNS for it to be significant - even if the intrinsic potency of Simufilam were high. (Pajouhesh et al., 2005).

3. Protein-Protein Interactions and FLNA Targeting

Simufilam is based on modulating protein-protein interactions, specifically between FLNA and Aβ. Protein-protein interactions are notoriously difficult to target with small molecules considering that these interactions usually involve large, flat, or irregular surfaces that do not have well-defined binding pockets.

The notion that Simufilam can precisely modulate the interaction between FLNA and Aβ oligomers is highly speculative. Even if Simufilam does bind to FLNA, the idea that this will result in therapeutically beneficial effects, without disrupting other essential FLNA functions (involved in cell structure, signaling, and migration), is not supported by evidence. Targeting protein-protein interactions is a challenging strategy with a high rate of failure in drug development, and Simufilam's mechanism does not address these difficulties convincingly.

Looking at this PPI inhibition allegedly done by Simufilam., multiple concerns must be raised regarding the efficacy of Simufilam. PPI drugs are notoriously hard to make, and when focusing on a neurodegenerative disease such as Alzheimer's the task only gets more challenging (Alzyoud et al., 2022).

Furthermore, the core challenges of a PPI inhibition drug for AD include identifying and validating the target, the PPI's structural complexity, dynamic design and conditions of protein structures, the off-target effects, BBB penetration, short half-life and tissue distribution, development of resistance to inhibition, and toxicity. After evaluating Simufilam's attempt to block the interaction between FLNA and α7 nAChR, an efficacy question regarding the drug's PPI may arise.

Firstly, designing a drug that targets protein-to-protein interaction is extremely difficult since these interactions frequently involve large, flat surfaces that prove to be hard to block with a small molecule drug such as Simufilam - lacking a clear binding pocket (Goncearenco et al., 2018).

Contrary to drugs that target enzymes or receptors that have well-defined active sites, PPIs are difficult to design and making them effective is also a challenge (Lu et al., 2020) .

Secondly, the inhibition of the FLNA-α7 nAChR interaction must not disrupt other essential PPIs or cellular functions. In this regard, Simufilam would need extensive tests to evaluate the specificity of the inhibitor and its impact on similar proteins or pathways that could be hindered (King et al., 2017). Acknowledging the concerning quality of these preclinical and clinical data, in regard to the retraction and multiple manipulations that Dr. Wang has been found guilty of (see section *All The Retracted Papers of Dr. Wang*), only a theorization can be made regarding the

impact of this inhibition on other pathways, some of which could be affected by Simufilam's alleged activity. In addition, the extended family of the nAChR could be affected by this binding. Knowing that the nAChR family may share similar binding motifs – even further complicating the action of Simufilam and its impact on Alzheimer's (IUPHAR/BPS Guide). Furthermore, the impact of α7 nAChR inhibition could hinder neurotransmission, and any inhibition could result in an unintended neurotoxic effect(s). Once more, this underlines the importance of rigorous preclinical research regarding the profile and mechanism of a drug.

Thirdly, for a PPI inhibitor such as Simufilam, to be effective it must be able to keep the PPI inhibited permanently – meaning that the bond should be covalent for the drug to be effective (Xie et al., 2023). Simufilam needs to permanently disrupt the protein-to-protein interaction to have deep long-lasting effects and not temporary effects. As Simufilam does not form a covalent bond, the FLNA – α7 nAChR interaction would not be permanently inhibited – lacking in therapeutic efficiency (Faridoon et al., 2023). This issue raises additional doubts about Simufilam's effectiveness, given that it would imply frequent dosing is needed to maintain any therapeutic effect - if any are present.

4. Naloxone Binding to FLNA and the VAKGL Peptide

Simufilam's interaction with FLNA involves the VAKGL peptide motif, which is present in the FLNA protein. Interestingly, Naloxone, an opioid antagonist, has also been shown to bind to FLNA at this site according to Dr. Wang. However, naloxone's binding to FLNA raises concerns about Simufilam's specificity and potential off-target effects. If Naloxone, a drug used for opioid overdose, binds at the same site as Simufilam, this overlap could lead to competition for binding or unintended interactions with other physiological pathways.

Furthermore, there is little evidence that modulating this interaction has a meaningful impact on Alzheimer's pathology. FLNA's involvement in Aβ toxicity remains speculative, and targeting a peptide like VAKGL may not significantly affect disease progression.

Looking at the 2008 study done by Dr Wang and Dr. Burns, they reported that Naloxone binds to FLNA with high affinity (Wang et al., 2008). This alleged binding is of great importance since it suggests a new pathway for a new drug such as Simufilam which could have similar effects – by disrupting FLNA's interaction with receptors such as α7nAChR. The research clearly indicates that the binding of Naloxone and Simufilam with FLNA is extremely similar, suggesting that Simufilam mimics Naloxone's targeting of FLNA. (Wang et al., 2008) (Wang et al., 2023).

Naloxone is an opioid antagonist mainly used to counteract the effects of opioid overdose (Wang et al., 2008). These effects are achieved by blocking the effects of opioids in the brain, to do so Naloxone acts as an antagonist, meaning that it blocks the opioid receptors in the brain. The discovery of Dr. Wang and Dr. Burns in 2008 was the starting point for new research on the role and impact that FLNA has in neurobiology and overall neurodegenerative diseases, such as Alzheimer's. The transition from Naloxone to Simufilam formerly known as PTI-125, was determined by the findings of misfolded FLNA in AD patients (Wang et al., 2012**)**. This misfolding of FLNA leads to toxic signaling pathways that are associated with amyloid beta increased level in AD patients. This theory and findings are not well research, and the core studies are from Dr. Wang – the 2008 study has been retracted and some other data too (see section *All The Retracted Papers of Dr. Wang*).

Now that the relationship background between Naloxone and Simufilam has been established, an assessment of the previous claims must be done. Previously stated, the only study that proves an alleged binding between FLNA and Naloxone has been made by Dr. Wang and Dr. Burns in their 2008 paper and has been retracted by PLoS editors (Wang et al., 2008). In addition, in the last 50 years no study has proved an alleged specific binding pocket for Naloxone in FLNA. Furthermore, Naloxone does not target tissues with high FLNA expression (Pert et Snyder, 1973). Thus, there is no compelling study that proves a binding site in FLNA for Naloxone.

VAKGL is a pentapeptide (5 amino acids) sequence derived from the protein FLNA (Wang et Burns, 2009).

No binding pocket was found near VAKGL in the structure of FLNA's dimerization domain (Lee et al., 2008). Furthermore, no model was ever proposed on the effects that an alleged binding of VAKGL may have on the overall structure and function of FLNA. Meaning that no evidence exists to prove that VAKGL binding could cause conformational change, overall changes or modulations in FLNA. Finally, VAKGL appears in many proteins, making this binding even more dubious. It is unclear why Naloxone would even bind specifically to FLNA - VAKGL, and not bind to other proteins with VAKGL, that are present in dozens.

Simufilam's finding was reportedly achieved through an in vitro screening assay where biotinylated VAKGL competed with FITC-tagged Naloxone for binding (Wang et Burns, 2009). This suggests that both Simufilam and Naloxone may have a similar target in regard to the binding site. This screening technique highlighted the potential ability for Simufilam to influence or modulate these interactions – selectively interact with specific tagged molecules. However, all these findings are uncertain, and considering the controversy surrounding Dr. Wang's work, as well as the fact that these hypotheses are based on a retracted paper, the results and final theories have yet to be proven and cannot be considered facts.

Following this, a group of researchers have made their own research to study and assess these claims (Heilbut et al., 2022). Questioning the evidence of the binding of Naloxone and Simufilam to VAKGL is a crucial issue, as without this alleged binding, no operation can be done and therefore no therapeutic effects could ever be achieved. To do this, they used the *Isothermal Titration Calorimetry* (ITC).

ITC is a laboratory technique used in the measurement of thermodynamics of interactions between molecules, such as binding affinity (Kd) (Measurlabs). It reflects how strongly the ligand binds to the target. ITC works by measuring the heat released or absorbed during the binding event in a solution. This provides a valuable take in the binding operation - how molecules interact on a biochemical level. Molecular interactions are governed by thermodynamic forces. Key contributors to non-covalent interactions include hydrogen bonding - *van der Waals forces* - hydrophobic effects, and entropy changes (Mukherjee et al., 2023). These forces collectively

influence the free energy change (ΔG) of the interaction, that the following equation represents: $\Delta G = \Delta H - T\Delta S$ (ICT) (Cooper, 1999)

- **ΔG** is the Gibbs free energy change, determining the spontaneity of the reaction.
- **ΔH** is the enthalpy change, reflecting the heat absorbed or released during bond formation.
- **T** is the absolute temperature.
- **ΔS** is the entropy change, representing the degree of disorder or randomness in the system.

As molecules bind heat is released and measured by the ITC procedure, if no binding is operated, the ITC experiment will also report it (Harvard Medical School). The results of this experiment proved no evidence of any binding of Naloxone or Simufilam to the target VAKGL – raising additional doubts on the mechanism of action of Simufilam.

See *Figure 2* for the graphical results. Here are the explained results: Firstly, the water + water interaction had no signal, as expected. Secondly, Acetazolamide + CAII had clear signal data of binding, pointing to a point where binding is saturable (meaning that there is a finite number of binding sites on the target molecule, and all the sites are occupied by the ligand). Thirdly, Naloxone + VAKGL peptide had no signal of binding, which is concerning. Finally, Simufilam + VAKGL and Simufilam + VAAGL (-ve ctrl) also had no signal of binding, which is logical since it theoretically mimics Naloxone's binding. (Heilbut et al., 2022).

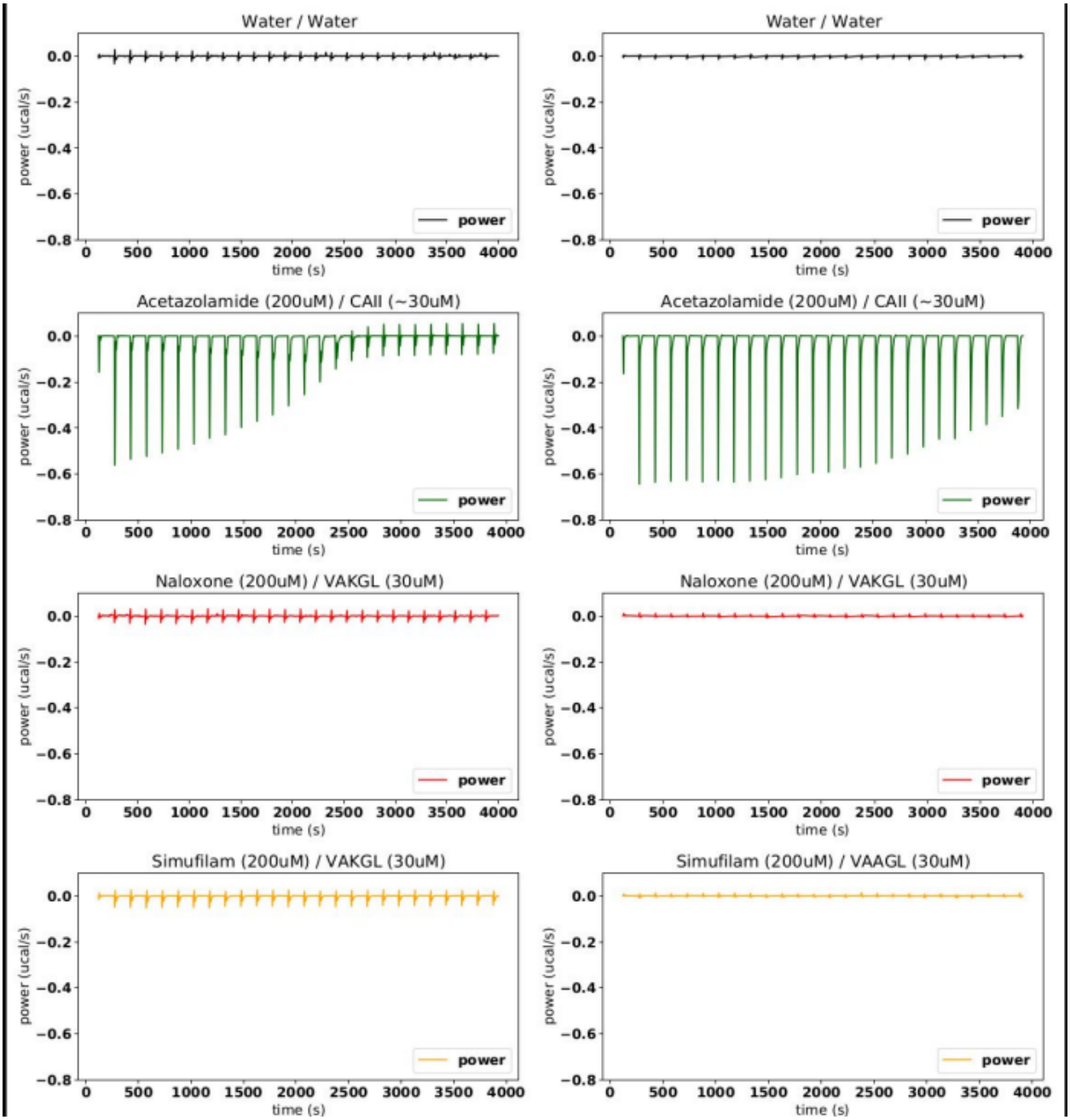

Figure 2. ITC Thermograms Results (Heilbut et al., 2022).

These data prove to be important since they demonstrate that no binding event occurred between Simufilam and VAKGL - its alleged target. (Heilbut et al., 2022). However, nothing is set in stone as this data is uncontrolled data and may be equally disrupted as Dr. Wang's 2008 study was. The situation remains unclear on this specific issue, as we have uncontrolled data on both ends. Still, the data from the ITC experiment must be assessed and considered as much as the 2008 study from

Dr. Wang. Acknowledging their limitations, particularly the 2008 study since proven to be fraudulent, unlike the ITC experiment.

Once again questioning the MOA of Simufilam and its existence – does Simufilam really have an MOA? For now, Simufilam's MOA is not understood to a level that can make it a Phase III reliable candidate drug according to our study, assessment and opinion. Nonetheless, Simufilam has deserved its Phase III trial, and we deeply hope that for Alzheimer's patients' sake it will find itself to be efficient, and this even if we do not see it as being efficient.

5. FLNA Discords and Its Use in Alzheimer's Disease

FLNA has diverse roles in cellular processes, from cytoskeletal structuring to signal transduction. It is not clear that misfolded FLNA plays a central role in AD. While Cassava Sciences proposes that Simufilam restores FLNA function, there is no established connection between FLNA misfolding and AD pathology. Independent studies have not validated the theory that targeting FLNA will improve cognitive function or reduce neurodegeneration in AD.

Moreover, FLNA is expressed in many tissues, and interfering with its function could cause unintended side effects. The broad physiological roles of FLNA raise concerns that Simufilam could disrupt essential processes unrelated to AD, further complicating its development as a safe therapeutic.

Simufilam was designed to bind FLNA, a protein that Cassava Sciences suspect to have an impact in AD. An in-depth look at FLNA, its relevance to AD and its link to Simufilam is crucial. FLNA plays a role in managing how substances move within the cells and how cells communicate with one another through signaling pathways (Razinia et al., 2023). The protein encoded by this gene is an actin-binding protein that crosslinks actin filaments and links actin filaments to membrane glycoproteins (Pollard, 2016). The encoded protein is involved in remodeling the cytoskeleton to effect changes in cell shape and migration (Seetharaman et al., 2020) (Fletcher et al., 2010). This protein interacts with integrins, transmembrane receptor complexes, and second messengers (Protein Atlas). Defects in this gene are a cause of several syndromes, including periventricular

nodular heterotopias (PVNH1, PVNH4), otopalatodigital syndromes (OPD1, OPD2), front metaphyseal dysplasia (FMD), Melnick-Needles syndrome (MNS), and X-linked congenital idiopathic intestinal pseudo-obstruction (CIIPX) (Medlineplus).

Furthermore, the FLNA gene provides instructions for producing the protein FLNA which helps build cells' extensive internal network of protein filaments called the cytoskeleton (Medlineplus, 2022). FLNA primarily binds to another protein called actin filaments and helps it form the branching network of filaments that make up the cytoskeleton (Lamsoul et al., 2020). FLNA can also bind to many other proteins in the cell to carry out various functions, including the attachment of cells to one another (cell adhesion), cell movement (migration), determination of cell shape, the relay of signals within cells, and cell survival (Welter et al., 2020) (Ketebo et al., 2021) (Lamsoul et al., 2020). These numerous functions involving FLNA have been found to play roles in regulating skeletal development, brain development, the formation of heart tissue, the formation of blood vessels, blood clotting, skin elasticity, maintenance of lung tissue, and the function of the digestive system. Additionally, FLNA is also involved in the organization of the extracellular matrix - a lattice of proteins and other molecules outside the cell (MedlinePlus). FLNA binds proteins called integrins which span the cell membrane and anchor cells to the extracellular matrix (Alberts et al., 2002). Through this binding, cells are correctly positioned, and signals can be exchanged between the cell and the extracellular matrix (Hynes et al., 2002). Following this, a question might arise, what are actin/micro filaments? Microfilaments are made up of two strands of actin proteins. These two strands are an important component of the cytoskeleton of a cell. Being flexible and relatively strong - situated in almost all eukaryotic cells - they are generally situated on the periphery of the cell. They have 3 core functions that are: cell mobility, cytokinesis, and change in cell shape. Moreover, concerning the structure of microfilaments, each component of the microfilament is known as globular actin. The globular monomer actin format called G actin is assembled into a polymer known as F actin (Filamentous actin format). The globular monomers assemble via their point end and barbed end to form an actin filament F actin, a faster growth is recorded at the barbed due to better connection. ATP binds to G-actin, then G-actins binds to ATPs where they create a nucleus - this process is called nucleation. This small nucleus then grows, adds more G-actin monomers, and elongates; this process is called elongation. The next phase is the steady-state, a phase where the F-actin strands do not have a net growth as they simply maintain

themselves. When growing (polymerization), G-actin binds to ATP, and when reducing its growth (depolymerization), G-actin binds to ADP.

The research concerning FLNA in AD provides concerning results, given that nearly all the research was done by Cassava Sciences under Dr. Wang. FLNA in AD is altered, while FLNA is typically an intracellular protein it plays a role in cell signaling by interacting with cell membrane receptors, where the extracellular Aβ42 can exert its influence (Burns and Wang, 2017). FLNA in AD is in an 'insoluble' form (Aumont et al., 2022). The functions of soluble FLNA are to maintain the cell structure and it is signaling under normal physiological conditions (Nakamura et al., 2011). Insoluble FLNA on the contrary is associated with disease states, particularly with AD. Insoluble FLNA aggregates and correlates with Aβ pathology level - potentially disrupting normal cellular functions (Aumont et al., 2022). In AD, FLNA becomes abnormally phosphorylated, leading to structural and functional changes (Aumont et al., 2022).

The only external research that indicates a potential link between FLNA and AD is a study that aimed to assess the levels of FLNA over the different stages of AD and to identify which AD-associated features were predicted by FLNA levels such as Aβ and Tau protein (Aumont et al., 2022). The study found a correlation between FLNA and Aβ levels. FLNA was positively associated with Aβ42 concentrations ($\beta = 0.406$, $p = 0.036$), see *Figure 3*. In contrast, the levels of insoluble FLNA were not significantly associated to Consortium to Establish a Registry for Alzheimer's Disease (CERAD) stages, see *Figure 4*. CERAD is a system used primarily to stage and assess the degree of AD pathology in brain tissue after death (CERAD).

Finding that insoluble FLNA levels rise at prodromal AD (early symptomatic stage), insoluble FLNA levels seemed to stabilize between the prodromal and ADD stages - suggesting that the increase occurs earlier and then plateaus. In ADD, soluble FLNA levels returned to normal, matching the stable insoluble FLNA levels. The soluble/insoluble FLNA ratio was significantly lower in the prodromal stage compared to non-AD subjects, suggesting this imbalance could indicate early AD. In addition, the presence of the APOE ε4 allele - a known genetic risk factor for AD - also influenced insoluble FLNA levels. APOE ε4 noncarriers with AD had significantly higher insoluble FLNA levels compared to non-AD subjects and APOE ε4 carriers. While FLNA

levels were not significantly different between APOE ε4 carriers and non-AD subjects. FLNA was a good predictor of prodromal AD among subjects with mild cognitive impairment (MCI), with an AUC of *0.818*. Insoluble FLNA did not significantly predict cognitive performance on any scales, meaning there was no strong link between FLNA levels and overall cognitive decline in AD patients. By contrast, Aβ42, neuritic plaques (NPs), phosphorylated tau (pTau), and total tau were all strong predictors of cognitive decline, especially in global cognition and memory – making them reliable biomarkers. Furthermore, insoluble FLNA was not correlated with synaptophysin - a protein that indicates synaptic integrity. Synaptophysin levels decrease in neurodegeneration, however this decline did not show any significant relationship with FLNA. Finally, insoluble FLNA levels showed no significant association with tau-related metrics including *Braak stages*, pTau, and total tau – suggesting no direct link between FLNA insolubility and tau pathology, see *Figure 5*.

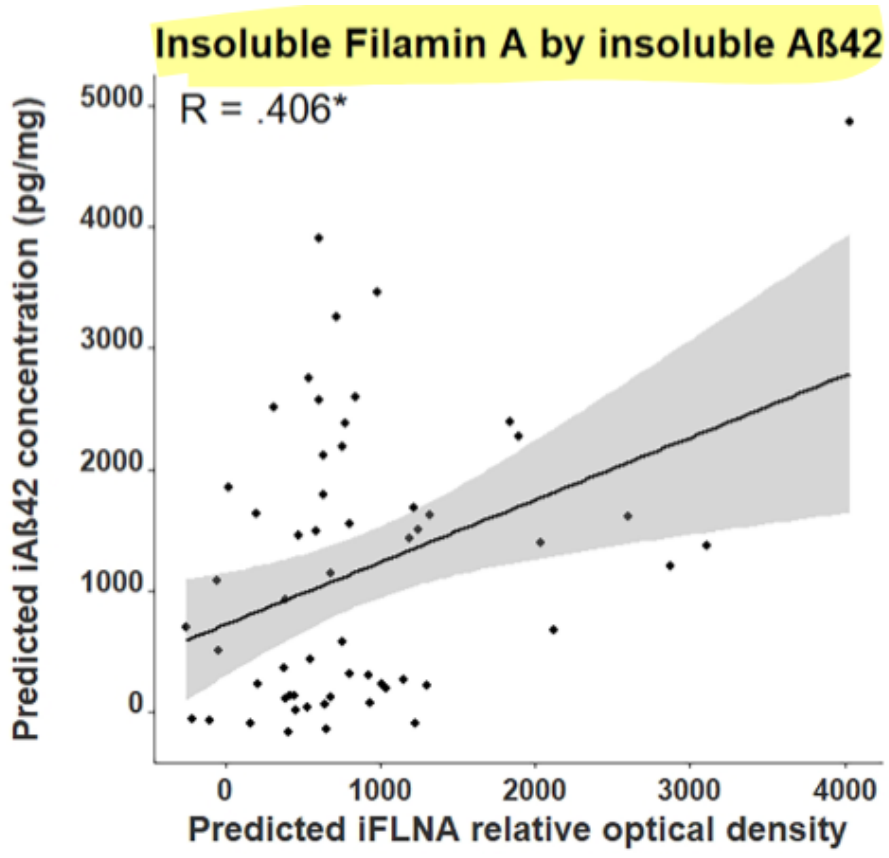

Figure 3. Associations between insoluble FLNA and Aβ-derived metrics (Aumont et al., 2022).

Disclaimer: This paper discusses our analysis of SAVA. It is important to disclose that we have a financial interest in this matter, as we will profit if the stock price declines.

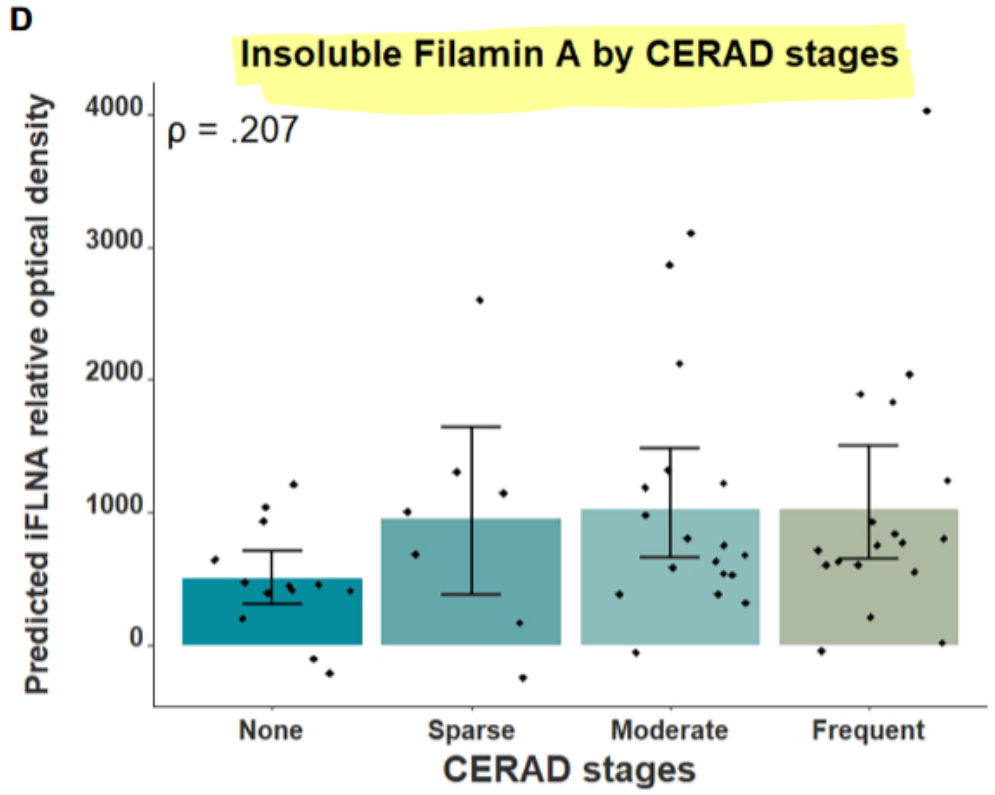

Figure 4. Associations between insoluble FLNA and CERAD stages (Aumont et al., 2022).

Dependent variable	Independent variable	Raw p-value	FDR-adjusted p-value	β/ρ
Insoluble Filamin A	$A\beta_{42}$	0.006	0.036*	0.406
	Neuritic plaques (log transformed)	0.017	0.042*	0.353
	Total tau	0.850	0.927	0.028
	Phosphorylated tau	0.978	0.978	-0.004
	Synaptophysin	0.275	0.367	0.219
	VAChT	0.146	0.218	-0.28
	ChAT	0.088	0.176	-0.335
	CERAD scale	0.122	0.209	0.207
	Thal stages	0.016	0.042*	0.318
	BRAAK stages	0.440	0.528	0.104
	ABC scale	0.017	0.042*	0.316
	Clinicopathological stages of AD	0.003	0.036*	0.386
$A\beta_{42}$	Total tau	0.004		0.401
	Phosphorylated tau	0.017		0.340
Neuritic plaques	Total tau	0.0003		0.494
	Phosphorylated tau	0.0001		0.524
Braak stages	CERAD scale	<0.0001		0.503
	Thal stages	<0.0001		0.596

Figure 5. Summary of statistical tests for all partial correlations adjusted for age, sex and study batch between biological measures and AD stages (Aumont et al., 2022).

Despite the correlation between FLNA and general AD progression scales, such as *ABC* and *AD clinicopathologic stages*, its transition to an insoluble form appears to follow the progression of Aβ pathology rather than tau mechanisms. The study suggests that while Aβ may trigger FLNA abnormalities - leading to its insolubility - this process is distinct from tau hyperphosphorylation and aggregation. Following this, a hypothesis can be made concerning FLNA insolubility, tau hyperphosphorylation, and aggregation, making them distinct events that are influenced by Aβ. "Following its structural alteration due to Aβ, we propose that FLNA would be more prone to a transition towards an insoluble state" (Aumont et al., 2022).

Upon evaluation of the presented data, our conclusion is that FLNA may have an impact on AD, and its link to Aβ is interesting. However, it still needs more studies to prove its importance in AD. Considering the current data, FLNA has not reached a sufficient level of understanding regarding its role in AD for us to deem it relevant - especially when evaluating it as a sole target to reduce or alter AD progression. A sane conclusion to have regarding FLNA's role in AD - given the current data - is that FLNA has little to do with AD although greater involvement could be discovered. Still, it would not be rational in our view to say that FLNA is the only protein that needs to be targeted to halt Alzheimer's progression. On that note, we conclude that FLNA has little to do with AD given the very low research data, that indicate any involvement in it. Furthermore, the potential impact that FLNA could have on Alzheimer's is too low to have a critical effect on the disease's progression in our view, considering the existing data. Solely targeting FLNA and its interactions is too small of an impact on such a complicated disease to be the sole contributor to its progression. The extent of FLNA's influence on AD is still very little understood, if not understood at all in our view.

6. Hyperphosphorylation: Not a Kinase-Targeting Drug

One of the hallmarks of AD is the hyperphosphorylation of tau proteins, which leads to the formation of neurofibrillary tangles (NFTs). The most successful efforts to develop AD drugs, now focus on tau pathology as a more promising target than amyloid.

Simufilam, however, does not target kinases or other enzymes involved in tau hyperphosphorylation. Without addressing tau hyperphosphorylation, Simufilam fails to intervene in one of the most significant drivers of cognitive decline in AD. This oversight significantly limits the drug's potential, as targeting amyloid without addressing NFTs has consistently failed to slow disease progression in previous trials.

Simufilam does not exert its effects through direct kinase activity or phosphorylation – so how does it do it?

When evaluating the MOA of Simufilam - its impact on the hyperphosphorylation of tau protein in Alzheimer's, and its effects on the Aβ42 - α7nAChR interaction. One must look at α7-nicotinic acetylcholine receptor (α7nAChR), an ion channel receptor that is part of the nicotinic acetylcholine receptors (nAChRs) family (IUPHAR/BPS).

α7nAChR is known for its high permeability to calcium ions (Ca^{2+}) (Shen et al., 2009) and plays important roles in neurotransmission, helping in the mediation of communication between neurons in the brain. (Natarajan et al., 2020).

The question remains: how does Simufilam's interaction with FLNA affect the relationship between α7nAChR and Aβ42? As explained in the section *Naloxone Binding to FLNA and the VAKGL Peptide,* FLNA can bind to various membrane proteins and receptors, this allegedly includes α7nAChR (Wang et al., 2023).

Thereby, FLNA acts as a scaffolding protein that helps organize the cytoskeleton and regulate signaling pathways (Deng et al., 2012). The alleged binding between FLNA and α7nAChR creates a modulation in the receptor's location, stability, and signaling (Burns and Wang, 2017).

Therefore, taking this into account, an assumption can be forged, that the disruption of the FLNA - α7nAChR interaction, allegedly caused by Simufilam could disrupt how α7nAChR behaves and reacts.

This would include the interaction it has with molecules such as Aβ42. Thereby explaining the change in toxicity (the toxicity of Aβ42 is explained in the section *Aβ42 Toxicity: Multiple Causes, No Direct Amyloid Clearance, and No Tau Solution*). Accordingly, this would explain the change in the α7nAChR - Aβ42 interaction. Knowing that α7nAChR state could lead – upon Simufilam's interaction – to a conformational state or localization in the membrane that could have an effect on its interaction with Aβ42 (Burns et al., 2023).

Conformational state: meaning that a protein can adopt different three-dimensional structures, that are called 'conformational state' (Monzon et al., 2016). These changes can occur in the case of binding to ligands, changes in pH, and post-translational modifications (Saio et al., 2015).

In addition, these changes in the structure can expose or hide specific binding sites, potentially leading to a change in the ability of the protein to properly interact with proteins, nucleic acids, or other molecules. This all depends on the binding site structure and arrangement. Therefore, ceasing FLNA - α7nAChR interaction could cause a change in the binding affinity, or ability to engage in specific molecular interactions that could either increase, or decrease for α7nAChR (Liang et al., 2016).

Regarding the binding affinity, in a conformational change or a change in the membrane position, both of those can affect the strength of an underlying binding such as the α7nAChR -Aβ42 interaction. (Feix et al., 2018).

One thing to keep in mind is that this remains highly theoretical and only reliable clinical data can assure us of any significance – which does not exist. The entire FLNA - α7nAChR - Aβ42 interaction, and relationship are still unclear as no data can entirely explain or show the effectiveness of Simufilam's MOA. All this theory is based on "alleged", "may", "could", and has no hard proof to explain or prove the MOA of Simufilam. Moreover, it is important to keep in mind that there is no external evidence of Dr. Wang's work to support his claims. In addition, when assessing his research, no clear explanation arises regarding Simufilam's MOA, the reason being that Cassava Sciences does not understand its own MOA. Alzheimer's itself is not well

understood and only adds uncertainty. Therefore, increasing our doubts on the MOA of Simufilam and its capability to achieve any statistical significances in those two-Phase III trials.

7. α7 Nicotinic Acetylcholine Receptor (nAChR) Drugs Have Already Failed in Alzheimer's Disease

Cassava Sciences claims that Simufilam reduces the toxic interaction between Aβ oligomers and α7nAChRs. However, drugs that target the α7 receptor - either as agonists or antagonists - have already been tested in AD and failed to show clinical benefits. Both α7nAChR agonists and inhibitors have been tested in clinical trials, but none demonstrated significant improvements in cognition or disease progression.

Given this history, there is no reason to believe that modulating α7nAChRs through FLNA will provide better results. However, Simufilam focuses on this pathway and ignores the overwhelming evidence that targeting α7nAChR in AD is not a viable therapeutic strategy.

α7nAChR is one of the core actors in Simufilam's alleged therapeutic effects. Therefore, the identification of α7nAChR is crucial. α7 nicotinic acetylcholine receptor (α7 nAChR) is a type of nicotinic acetylcholine receptor (nAChR), which is part of a family of ligand-gated ion channels. Acetylcholine receptors (AChRs) are functional elements of the cholinergic system studied for their potential therapeutic effects in Alzheimer's (IUPHAR/BPS).

AChRs are distributed roughly in all regions of the brain (Henderson et al., 2015), while nAChRs are mostly found in the central nervous system (CNS). The composition of neuronal nAChR is made up of two subunits, α and β; they assemble and form either a heteromeric or a homomeric arrangement (Gay and Yakel, 2007). α7 is one of the subunits that has been identified in brain tissues (Millar, 2008) and is one of the subtypes most heavily involved with neurological diseases such as Alzheimer's (Terry et al., 2023).

A7nAChR is activated by acetylcholine (ACh), which is responsible for the cholinergic signaling in the brain. ACh can bind to receptors and will open a pathway that allows ions - mostly calcium (Ca^{2+}) - to enter the neuron. Furthermore, α7nAChR is mainly present in the cortex, hippocampus – CA1- CA3 and dentate gyrus regions (Picciotto et al., 2001) – those regions are associated with cognition, memory, and learning (Leanza et al., 1996). Making α7nAChR a potential target for cognitive decline associated with Alzheimer's.

An interesting paper was published in 2024 (Crestini et al., 2024); it assessed and accounted for all the clinical trials that included nAChR as a target for an Alzheimer's drug – whether finished or in progress. The focus of the paper was to assess the safety profile and efficacy profile of nAChR in Alzheimer's - as a target. The study used *39* trials in which nAChR was a target for an Alzheimer's drug - the majority were Phase II trials.

Firstly, evaluating the safety profile of nAChR when activated or inhibited by drugs for Alzheimer's. They reported that "no concerns appear to have been raised on their tolerability, expect for some sporadically occurring gastrointestinal disorders." (Crestini et al., 2024).

In addition, when assessing the safety profile of Simufilam - which is included in their paper – Cassava Sciences reported on their Phase II a good safety profile with no major events. Therefore, it would be wise to say that the safety profile of nAChR and therefore Simufilam in Alzheimer's is good.

Secondly, when they evaluated the efficacy of nAChR, either activated or inhibited by a drug aimed at Alzheimer's, the results were not as fruitful as those for the safety profile. Indeed, as the data reported "confirm that the lack of success in clinical efficacy is the main reason, which led to discontinuation of research on this class of drugs". α7nAChR being no exception in this statement, the clinical safety is confirmed; however, the potential for action and therapeutic effects when implicating α7nAChR as a main actor in a drug aimed at Alzheimer's proves to be statistically and clinically insignificant. See *Figures 6 and 7* for more comprehensive data on the *Therapeutic Effect Summary*.

Thirdly, the paper includes an interesting point that should be noted as relevant to our understanding of nAChR when inhibited or activated by a drug aimed at Alzheimer's. In their conclusion, they included the opinion that further investigation in high-quality trials would be needed to assess the true extent of nAChR and its potential use as an Alzheimer's drug. The need for high-quality trials is crucial since the available data pool is relatively small. Therefore, it cannot lead to a conclusive, evidence-based evaluation of nAChR efficacy as a target candidate in Alzheimer's.

Molecule	Mechanism of Action	Therapeutic Effect Summary
Nicotine	- nAChrs agonist - stimulation of nAChRs in the central nervous system, which regulates the release of various neurotransmitters, such as dopamine, glutamate, serotonin, norepinephrine and γ-aminobutyric acid	In mild-to-moderate AD, the trials show a small effect on attention. However, no improvement was reported on memory, behavior and global cognition. Preliminary evidence shows a potential effect of nicotine on cognitive functions in people with MCI.
ABT-089	- selective neuronal nicotinic receptor (NNR) modulator - acts as an α4β2-nAChR partial agonist to stimulate the release of [3H]-dopamine	No improvement reported in mild-to-moderate AD.
AZD3480	- selective neuronal nicotinic receptor modulator - as an agonist, it has greater affinity for the α4β2 receptor than for the α7 receptor	One trial failed to show efficacy in reducing cognitive decline. However, some effect was reported in secondary outcomes (MMSE, ADCS-CGIC).
Varenicline	- nicotine bioisostere - stimulates the release of dopamine and reduces the self-administration of nicotine. Additionally, due to its characteristics, it is used as a pharmacotherapy for smoking cessation.	In one study, a single dose (1 mg BID for 4 weeks) showed no effect on memory, behavior and global cognition.

Figure 6. Synopsis of the mechanisms of action and therapeutic effects of the major nAChR agonists, as reported in published clinical trials (Crestini et al., 2024).

Molecule	Mechanism of Action	Therapeutic Effect Summary
ABT-126	- partial agonist of α7 nAChR - has been shown to exhibit a maximum agonist activity of 74% in the human form of the α7 nAChR receptor	Different drug doses (5, 10, 25, 50, 75 mg) showed no statistically significant ability to reduce cognitive decline in mild-to-moderate AD.
ABT-418	- nicotine bioisostere - has greater selectivity for the α4β2 nicotinic receptor subtype and produces some in vitro effects similar to those produced by nicotine	Some effect was reported in different verbal learning and retrieval scores (selective reminding task: total recall; selective reminding task: recall failures), but the effect in several areas of memory impairment in dementia has yet to be tested.
PTI-125	- binds the scaffolding protein filamin A - reduces Aβ1-42's binding affinity for a7nAChR, thereby preventing Aβ1-42's signaling and further accumulation on a7nAChRs. It can prevent and reverse the binding of Aβ1-42 to α7nAChR.	An improvement in some biomarkers (total tau, p-tau181, neurofilament light chain, neurogranin, YKL-40, IL-6, IL-1β and TNFα) associated with AD was reported. The effects on cognitive decline are undergoing assessment, although the preliminary results seem encouraging.

Figure 7. Synopsis of the mechanisms of action and therapeutic effects of the major nAChR agonists, as reported in published clinical trials (Crestini et al., 2024).

No clinical or statistical efficacy has been shown by either inhibiting or activating nAChR in Alzheimer's. Moreover, the conclusion that we have drawn after evaluating this data is that targeting nAChR can be useful - especially α7nAChR, which is involved in cognitive functions - but it cannot be the main actor in the treatment. Still, it can act as a robust contributor to a multi-targeting Alzheimer's drug. We find ourselves once again skeptical of Simufilam's efficacy when taking this additional data into account. Making an impact on Simufilam's credibility as a candidate drug in Alzheimer's.

8. Aβ42 Toxicity: Multiple Causes, No Direct Amyloid Clearance, and No Tau Solution

Simufilam's mechanism relies on reducing the neurotoxic effects of Aβ42. However, Aβ toxicity arises from multiple causes, including oligomer formation, plaque accumulation, and interactions

with other proteins. Simply modulating one interaction is unlikely to address the broader pathology of Aβ in AD. Moreover, Simufilam does not directly clear amyloid plaques, a key target in AD treatment.

Even if Simufilam successfully reduced some Aβ toxicity, it does not address NFTs or neuroinflammation, which are critical contributors to cognitive decline. Without a tau-targeting strategy, or a mechanism to clear amyloid, Simufilam's therapeutic potential is severely limited.

A main component of Alzheimer's is Aβ42 - a 42-amino acid long peptide (Zhang et al., 2023). Two main types of amyloid beta (Aβ) peptides exist, Aβ42 and Aβ40 - both derived from the amyloid precursor protein (APP) (Chen et al., 2014). Aβ42 is the major component of amyloid plaques found in the brains of Alzheimer's disease patients. Aβ42 toxicity in Alzheimer's is complex and has multiple pathways and mechanisms that cause the underlying toxicity that is observed (Lim et al., 2007).

As written in the *Simufilam's Proposed Mechanism of Action* section of this paper, Simufilam aims to restore FLNA's initial shape and function. By stabilizing FLNA, Simufilam seeks to correct the toxic effects that arise from α7nAChR - Aβ42 binding (Wang et al., 2023). However, multiple issues arise when evaluating this approach regarding its efficacy on AD.

Firstly, Simufilam has a major limitation that could have a grand impact on its efficacy and impact on Alzheimer's. The drug does not promote any clearance of Aβ42 or amyloid plaques. Amyloid plaques are a great part of Alzheimer's, and their clearance has been of major concern in the development and design of existing and new drug candidates for Alzheimer's (Zhang et al., 2023). The fact that Simufilam does not have any direct clearance effects on amyloid plaques is a great limitation for the drug. Without addressing the amyloid plaques issue, Simufilam disregards the accumulation of Aβ42 as insoluble plaques and could therefore allow a buildup of it. Moreover, this buildup of the amyloid plaques would signify an increase in overall neurotoxicity and inflammation (Azargoonjahromi, 2024). Simufilam's lack of amyloid clearance indicates an inability to remove Aβ42, which could mean that Aβ42 may remain active even when Simufilam is present in the brain.

Secondly, the toxicity of Aβ42 is multifactorial in nature, and simply stopping the α7nAChR - Aβ42 interaction would not eliminate the total toxicity of Aβ42 (Moore et al., 2018). Therefore, it proves the inefficacy of Simufilam in Alzheimer's. Knowing that the alleged interference of Simufilam between α7nAChR and Aβ42 would not stop the toxicity of Aβ42, even if the drug were to work as promoted by Cassava Sciences.

Simufilam focuses on the FLNA - α7nAChR - Aβ42 interaction and its impact on Alzheimer's. However, it is not sufficient to focus solely on this mechanism of Aβ42 toxicity, since Aβ42 exerts its toxicity through multiple channels, and stopping just one of them (α7nAChR) might not be enough to protect against neuronal damage and the overall damage caused by Aβ42 in Alzheimer's (Azargoonjahromi, 2024).

Furthermore, Alzheimer's, being a complicated disease, might require combined therapy to have a full effect, considering that it is a multi-factorial disease (Carreiras et al., 2013). Multiple therapeutic agents composed of amyloid clearance, reduction of tau pathology, and additional mechanisms of Alzheimer's disease could be the solution; still, this is only a theory.

Thirdly, Simufilam's limited efficacy on microglial activation is also a critical limitation. Although Simufilam claims to have some anti-inflammatory effects, it does not cover the full scope of the effects (Meraz-Rios et al., 2013). It does not directly target chronic neuroinflammation, which is in most cases associated with Aβ42 accumulation. The importance of this is that chronic neuroinflammation increases neurodegeneration and contributes to cognitive decline (Chen and Yu, 2023) (Zi-Zhen et al., 2023). This grave issue is not adequately addressed or focused on by Simufilam, which makes it an even less eligible candidate, as it does not affect neuronal death that occurs in Alzheimer's (Takuma et al., 2004). In addition, Simufilam has been shown to be ineffective against inflammatory cytokine release. The release of pro-inflammatory cytokines in response to Aβ42 accumulation, and the increase level of amyloid plaques that occurs in Alzheimer's is not challenged by Simufilam. Thereby allowing neuroinflammation to continue its growth and impact.

Fourthly, when evaluating the efficiency of Simufilam in relation to synaptic damage that occurs in Alzheimer's disease. Simufilam allegedly partially improves synaptic function through its effects on FLNA (Wang et al., 2023). However, it may not fully restore synaptic integrity or restore it at all, given the remaining high levels of Aβ42 caused by its non-clearance. Despite the alleged FLNA stabilization, some Aβ42 toxicity could remain. These toxicities could cause disruption of synaptic signaling and the receptor internalization. In addition, the limited efficacy that Simufilam has on oligomer toxicity, such as Aβ42, can lead to synaptic damage in Alzheimer's. (Barucker et al., 2015). The sole action of Simufilam on FLNA, even if successful, would not be sufficient to nearly counteract the multiple damaging effects of Aβ42 oligomers on synapses. (Takahashi et al., 2004). Therefore, Simufilam is prone to inefficacy concerning synaptic damage.

Fifthly, Simufilam provides no clear proof of a solution for tau pathology. The tau pathology involves hyperphosphorylation of tau protein and increased levels and aggregation of the tau protein; this leads to the formation of neurofibrillary tangles (NFTs) (Miao et al., 2019). NFTs have a decisive role in the development of Alzheimer's with Aβ - as they are the hallmarks in Alzheimer's (Mahaman et al., 2021). Besides, Simufilam does not engage in the blockade or reduction of tau hyperphosphorylation. This lack of impact on tau hyperphosphorylation or aggregation is a critical limitation for Simufilam's efficiency, as tau proteins are among the main contributors to Alzheimer's (Korgiopoulou, 2020).

Moreover, regarding the non-impact of Simufilam on tau pathology, it does not directly inhibit any enzymes involved in the phosphorylation of the tau protein. Some of these enzymes are GSK-3β (glycogen synthase kinase-3 beta) and CDK5 (cyclin-dependent kinase 5) (Xia et al., 2021). Not targeting these kinases means that Simufilam does little to none to prevent the formation and development of NFTs. Therefore, the tau pathology will most likely continue its progression, even if the amyloid toxicity is reduced (Knox, 2022).

To conclude, Simufilam has an overall low efficacy from data that has been reported both from Cassava Sciences and other relevant scientific papers. Simufilam does little to none to prevent the accumulation of the two main hallmarks of Alzheimer's, which can only lead to an efficacy failure for Simufilam in this Phase III trial, in our view.

9. Dimebon Phase III Failure: A Cautionary Tale

The failure of Dimebon in its Phase III clinical trial serves as a cautionary example for Simufilam. Dimebon was initially believed to offer significant cognitive benefits in AD, but subsequent trials revealed no efficacy. Simufilam faces similar risks, as its early-stage data is based on open-label studies with inherent biases and methodological weaknesses.

Just like Dimebon, Simufilam is at risk of showing early promise – even if they are not really promising as the data is weak - only to fail in the rigorous Phase III trials. The lessons from Dimebon underscore the importance of skepticism regarding small-scale, uncontrolled studies in AD drug development.

Dimebon or formerly Latrepirdine is a drug that was initially developed and launched in the late 1980s in Russia as an oral antihistamine for allergy treatment. The drug blocked the H1 histamine receptors with high affinity and was used in doses of 10-20 mg, 2-3 times per day (Bezprozvanny, 2010). Later, it was discovered that the drug could be beneficial in treating neurodegenerative diseases such as Alzheimer's. In 2008 Dimebon had a Phase II trial for Alzheimer's, and the results were astonishing. It was a small placebo-controlled trial, with 183 patients, that had mild to moderate Alzheimer's disease. The results for this trial were promising, with improvements in cognitive function and overall efficacy in comparison to placebo (Jones, 2010). The precise results are the following:

- ADAS-cog score (Alzheimer's Disease Assessment Scale-cognition), the mean drug-placebo difference was -4.0 with $p < 0.00011$.
- For the MMSE (Mini-Mental State Examination), the mean drug-placebo difference was 2.2 with $p < 0.00011$.
- For the CIBIC-plus (Clinician Interview-based Impression of Change plus Caregiver Input), the mean drug-placebo difference was 0.6 with $p < 0.0001$.

Furthermore, Dimebon appeared to stabilize symptoms, or even improve them in patients over a one-year period. After this successful trial, Pfizer sought to establish a partnership with Medivation, which was achieved in September 2008 (Bezprozvanny, 2010).

However, in the Phase III CONNECTION trial of 2010, all went rogue. It was a multi-center, double-blind, placebo-controlled study involving 598 patients, with mild to moderate AD. The trial was conducted jointly by Pfizer and Medivation. The objective of the trial was to confirm the results of the Phase II trial and determine if Dimebon could improve cognitive and functional outcomes - very similar endpoints to the ongoing Phase III trials of Simufilam.

The results of this Phase III trial were not statistically significant on any scale or assessment of Alzheimer's disease advancement. There was no increase in the placebo group, and no improvement in cognition or functioning was observed in patients in the Dimebon Phase III trial (Pfizer Press Release, 2010).

The explanation for this large difference between the Phase II and Phase III trial results.
Firstly, the MOA of Dimebon, which was said to protect mitochondrial function and stabilize neurons, was not logical and little understood – the MOA was unclear and confusing (Jones, 2010). Therefore, when it was tested on a larger, broader population, Dimebon was not effective. The weaknesses in the MOA led to the inefficacy of Dimebon on the numerous and complex Alzheimer's pathologies.

Additionally, it could also be that the pathology that Dimebon aimed to target was simply not relevant enough to influence a larger population of patients. Subsequent studies were done after the failed Phase II trial to evaluate Dimebon's MOA, and it was found to be much weaker than originally thought.

Secondly, the Phase II trial had a small patient population and was a single-country study. In comparison, the Phase III trial CONNECTION had a much larger patient population and was multi-centered. Earlier, smaller trials are prone to have higher levels of well-responding patients compared to larger trials, where the participants are more diverse (*BMJ* 2013;346:f2304). In

addition, Phase II trials have higher controls on the patient population (who they include in the study and who they exclude) than larger trials do; this also influences the Phase II data and its relevance. The larger trials, such as CONNECTION, provide reliable and generalized data for the drug's effectiveness; the random effect in the Phase III trial disappears.

When comparing Simufilam's Phase II results - see section *Probability of Success in Phase III Given Phase II Failure* - to those of Dimebon, we can see that the results of Simufilam are vastly weaker. Still, the bull community holds faith that the Phase III trial results will come out successful.

In addition, Simufilam Phase II trial is an open label and randomized trial. The 6-month randomized results are in no way statistically significant and the data from the open-label period are not conclusive to be considered significant. Additionally, an open label data is highly unreliable, and no true analysis nor conclusion can be based on these data (Day and Williams, 2007). Therefore, only the randomized part of the trial is worth analyzing, and when analyzed, the trial's results can be considered insignificant.

Simufilam has a MOA that is not fully understood and therefore could face some difficulties regarding its efficacy in the Phase III trial – considering that the patient population and diversification is much higher than in the Phase II trials. Additionally, the patient population has not been handpicked in contrary to a Phase II trial. Therefore, the random effect in the Phase III trials will disappear, and the true results will emerge - according to our evaluation will prove that Simufilam is not effective in Alzheimer's.

Conclusion

To conclude, this part on the scientific approach and mechanism of action of Simufilam. We evaluated that the drug may have some effects, however those effects even if achieved would be too small to have a true and lasting impact on Alzheimer's. Furthermore, Simufilam has significant deficiencies in its MOA, and it is not even clear if the alleged MOA works. Therefore, it would

not be wise or evidence-backed to make a statement that Simufilam is going to work on Alzheimer's patients. The stabilization or reduction of the advancement of the disease is highly improbable. It would not be a well-supported decision to bet on the results of the ongoing Phase III trial of Simufilam as being statistically or clinically significant. Our exact prediction in percentage value of probability for success and failure is written in the section *Simufilam's Probability of Success*.

Probability Analysis: Quantifying the Likelihood of Simufilam's Failure

The challenge with evaluating Simufilam, the drug developed by Cassava Sciences, lies not in the intuitive understanding that it is unlikely to demonstrate statistical significance for its primary endpoint, but in the rigorous task of quantifying this failure. While it may seem self-evident from our analysis that Simufilam will be ineffective, translating this intuition into a formal, quantifiable probability model is far more complex. This complexity is reminiscent of *Leibniz's* efforts to mathematically prove that 2+2 equals 4 - what appears to be common sense becomes intricate when subjected to formal demonstration.

In our case, the task is made even more difficult with the allegations of data manipulation surrounding Simufilam's clinical trials. Manipulated data introduces uncertainty, making it unreliable for statistical modeling. When working with manipulated data, the results can no longer be trusted, since the underlying information has been compromised. The difficulty compounds when multiple questionable datasets are aggregated to form a probability model; the inaccuracies build upon each other, making it impossible to reach a sound conclusion.

Therefore, to ensure the robustness of our analysis, we will proceed with the 'purest' form of mathematics to demonstrate, step by step, that Simufilam is unlikely to succeed. Our analysis employs a *Conditional Probability Model* to provide a nuanced view of Simufilam's likelihood of success in Phase III trials. This model goes beyond binary predictions, using interconnected probabilities to gauge the likelihood of achieving the trial's primary endpoint. Each component's success depends on the preceding conditions, allowing a comprehensive analysis based on four critical factors:

1. Target Validity P(T)
2. Drug Design P(D)
3. Phase III Success Given Phase II Failure P(PS3)
4. Design of the Phase III trial P(P3D)

$$P(S) = P(T) * P(D) * P(PS3) * P(P3D)$$

1. Probability of FLNA as a Target for AD

To rigorously evaluate the probability that FLNA is a viable therapeutic target for Alzheimer's Disease, we developed a conditional probability model. Although initial evidence suggests limited effectiveness, translating this insight into a formal, quantifiable probability model is complex. Like *Leibniz's* work to prove basic arithmetic, formalizing intuitive beliefs about FLNA's limitations requires precision, especially when faced with uncertainties in available data.

Our method integrates a weighted probability system across five critical factors, each influencing FLNA's likelihood of being a valid target. This conditional probability framework is effective because it:

1. Encompasses Multi-Dimensional Data: AD is a complex disease, involving multiple pathways and biomarkers. By assigning each factor a probability score, we avoid the

oversimplification seen in single-factor models and account for the diverse, albeit limited, evidence related to FLNA's role.

2. Provides Clear Quantitative Outcomes: Each probability score is multiplied, making the model sensitive to variances across factors. This cumulative structure provides a mathematically rigorous approach to conditional probability, where lower scores in any factor significantly impact the final result. This conservatism is crucial in fields like AD research, where overestimating therapeutic potential can lead to costly and ineffective trials.
3. Mitigates Bias from Unverified Data: Incorporating independent validation (IV) minimizes reliance on data from Cassava Sciences. Without accounting for this, probability models could inflate FLNA's viability due to the limited diversity of data sources.

Alternative models, such as non-weighted averages or qualitative assessments, suffer from significant drawbacks when applied to probabilistic determinations of therapeutic targets:

1. Single-Factor or Unweighted Models Lack Nuance: If we were to average the scores of each factor without weighting or combine them in a simplistic manner, the model would ignore essential variability across factors. For example, it would overlook the fact that the weak association with cognitive decline (PPCD = 0.1) should lower the overall probability more than independent validation (IV = 0.3) alone.
2. Over-Reliance on Strong Associations: Relying solely on strong markers, such as Aβ (0.45), while ignoring weaker ones, could create a falsely optimistic probability score. Our cumulative approach avoids this by ensuring that weak evidence in any one area diminishes the overall score accordingly.

First, we need to define and weight each of five factor that contributes to the fact that FLNA is a potential target for AD or not. So, we will be assigned for each factor a probability score (0–1) to quantify support for FLNA as a target. This approach is nuanced, allowing each component's probability to affect the final likelihood:

Pathogenic Link Validity (PLV)

Measures the extent to which FLNA is implicated in AD pathology, such as associations with amyloid-beta (Aβ42) and tau proteins. There is limited evidence which suggests a weak connection.

$$\text{PLV} = 0.3$$

Independent Validation (IV)

Evaluates whether independent studies support FLNA's role in AD, minimizing biases from single-source studies. Since most data originates from Cassava Sciences (6 out 14 research papers), with little independent replication.

$$IV = 0.3$$

Predictive Power for Cognitive Decline (PPCD)

Assesses if FLNA levels correlate with cognitive decline stages in AD. Minimal association with cognitive decline.

$$PPCD = 0.1$$

Association with Aβ (Aβ)

Assess if FLNA is correlates with the most prominent hallmark of AD, Aβ42. There are some correlations.

$$\text{A}\beta = 0.45$$

Association with Tau (AT)

Assess if FLNA is correlates with the hallmark that is associated with cognitive decline, Tau. There are no correlations between Tau and FLNA.

$$AT = 0.05$$

Potential Side Effects (PSE) w0.1

Considers FLNA's systemic roles, where high scores indicate a lower likelihood of off-target side effects.

$$PSE = 0.8$$

The combined probability $P(FLNA)$ of FLNA being a valid target, given the observed values of each factor, is:

$$P(FLNA) = PLV * IV * PPCD * \text{Aβ} * \text{AT} * \text{PSE}$$

$$P(FLNA) = 0.3 * 0.3 * 0.1 * 0.45 * 0.05 * 0.8$$

$$P(FLNA) = 0.000162 = 0.0162\%$$

This outcome supports our initial hypothesis that FLNA is a statistically unlikely target for AD, given the currently available evidence. The combined score (0.0162%) is both mathematically sound and self-explanatory, offering transparency in how each factor contributes to the conclusion. This structured approach, built on conditional probability, provides a defensible, bias-resistant evaluation, minimizing the likelihood of overstated results.

In essence, our method exemplifies a rigorous mathematical process - ensuring that conclusions about FLNA as an AD target withstand scrutiny and remain aligned with empirical evidence, thus making it the most reliable approach to evaluate FLNA's therapeutic potential for AD.

2. Probability that Simufilam is Correctly Design to Do What it is supposed to do P(D)

Instead of applying a conditional probability model to evaluate Simufilam's design suitability for AD, a more straightforward, factor-based probability assessment is appropriate. Conditional probability models are well-suited for evaluating systems with dependent variables where the outcome of one factor meaningfully affects the probability of the others. However, in the context of drug design, especially for neurodegenerative diseases, the efficacy of each design feature is not interdependent in a way that conditional probability would capture accurately.

Each design factor (such as LogP, metabolic stability, and specificity) contributes independently to the drug's overall effectiveness but does not directly influence the probability outcomes of the other factors. For example, a favorable LogP value does not increase or decrease the likelihood of Simufilam having sufficient metabolic stability. Therefore, assuming conditional dependence among these design attributes could obscure the actual, independent influence of each factor on the final outcome.

Thus, a more representative model uses an average probability based on individual scores for each of five key factors. This approach scores each factor independently from 0 to 1 based on existing data, then averages these scores to calculate a simple, non-conditional probability of Simufilam meeting its intended therapeutic design goals:

1. LogP and BBB Penetration Validity (LPV): Measures the suitability of Simufilam's LogP for BBB penetration. With a LogP value of 1.1, which is relatively low, Simufilam may struggle to cross the BBB efficiently.

$$LPV = 0.75$$

2. Metabolic Stability (MS): Assesses Simufilam's half-life and stability. With a half-life of 4.5 hours, the rapid clearance could hinder sustained efficacy, as frequent dosing might be required.

$$MS = 0.8$$

3. Protein-Protein Interaction Validity (PPIV): Evaluates Simufilam's ability to modulate the interaction between FLNA and Aβ. This interaction remains speculative, given the absence of conclusive data on Simufilam's precise binding efficacy.

$$PPIV = 0.3$$

4. Specificity and Off-Target Effects (SOTE): Considers risks of off-target binding, especially with Naloxone sharing potential binding sites. Lack of specificity may reduce efficacy or lead to unintended interactions with other receptors.

$$SOTE = 0.10$$

5. Efficacy in Target Mechanisms (ETM): Measures effectiveness based on Simufilam's impact on core AD pathology, including amyloid and tau involvement. With no clear amyloid clearance or tau modulation, its efficacy remains uncertain.

$$ETM = 0.25$$

Using these factors to calculate the probability of P (D):

$$P(D) = \frac{LPV + MS + PPIV + SOTE + ETM}{5}$$

$$P(D) = \frac{0.75 + 0.8 + 0.3 + 0.1 + 0.25}{5}$$

$$P(D) = \frac{2.2}{5} = 0.44 = 44\%$$

This approach provides a realistic, quantifiable assessment of Simufilam's potential design success without the assumptions inherent in a conditional probability model. The result is a clearer view of how each factor independently contributes to the drug's likelihood of achieving its therapeutic aims in AD.

3. Probability that a Failed Phase II Succeed in Phase III

Estimating the POS in a Phase III trial after a Phase II failure, represented as P(PS3), poses significant challenges. When a drug fails to meet its primary endpoint in a controlled Phase II trial, the likelihood of Phase III success is generally diminished. Historically, drugs entering Phase III after successful Phase II trials have a success rate of about 58%, but when Phase III proceeds despite a Phase II failure, the expected success rate drops markedly. Here, we aim to quantify this reduced probability with analytical rigor, using Simufilam's Phase IIb trial as an example.

To estimate P(PS3), we consider the general success rates alongside Alzheimer's-specific data:

Historical Baseline Success Rates:

$$General\ Phase\ II\ Success\ Rate: \sim 30.7\%.$$

$$Phase\ III\ Success\ After\ Phase\ II\ Success: \sim 58.3\%.$$

Severity Factor α:

- α accounts for Phase II failure severity, scaling success probability for Phase III:

- Moderate Failure (e.g., Simufilam): α=2
- Severe Failure: α=3
- Near-Miss Failure: α=1.5

Risk Adjustment Factor R:

General Probability Model (Non-AD):

$$P(P3|FP2) = P(SP3) * \frac{1}{\alpha}$$

For Simufilam's moderate failure:

$$P(SP3) = 0.583, \alpha = 2$$

Estimated Probability for Non-AD Drugs:

$$0.583 \times \frac{1}{2} = 29.15\%$$

Alzheimer's-Specific Model Adjustment:

AD Phase III Success Rate (Kim et al., 2022):

$$Estimated\ at\ 2\%$$

Moderate Failure (Simufilam) For AD:

$$\mathrm{P(SP3, AD)} = 0.02, \alpha = 2$$

Adjusted Probability for AD Drugs:

$$0.02 * \frac{1}{2} = 1\%$$

Weighted Average for AD Context:

Combining AD and general therapeutic probabilities, weighted $\frac{2}{3}$ for AD and $\frac{1}{3}$ for general:

$$P(PS3) = \left(\frac{2}{3} * 0.01\right) + \left(\frac{1}{3} * 0.2915\right) = 5.19\%$$

Given the complexities of AD and the moderate Phase II failure of Simufilam, our model estimates a 5.19% probability of success in Phase III. This calculation highlights the substantial challenges in advancing to successful late-stage trials after a Phase II failure in AD.

4. Probability that Simufilam's Phase III Trial is Suitably Designed for Demonstrating Efficacy P(P3D)

To assess the probability that Simufilam's Phase III trial is designed effectively to showcase therapeutic efficacy, a factor-based probability model is appropriate. Unlike conditional probability models, which are more applicable to systems with interdependent outcomes, each trial design factor here contributes independently to the overall likelihood of demonstrating efficacy without directly influencing other factors. This approach considers the individual impact of each factor on the trial's success potential, providing a straightforward and non-conditional probability calculation.

Each key factor of the trial design—such as endpoint relevance, sample size adequacy, and patient population—has been scored independently on a scale from 0 (poor) to 1 (excellent). These scores are averaged to determine the probability P(P3D), representing the likelihood that the design supports achieving the desired clinical outcomes.

Key Design Factors and Scores

1. Primary Endpoint Relevance (PER): The trial uses ADAS-Cog12, a cognitive assessment tailored to Alzheimer's disease, to measure cognitive and functional decline over 52 weeks.

$$PER = 0.9$$

2. Statistical Power and Sample Size (SPS): With 750 randomized participants (1:1 allocation), the trial's design maximizes statistical power.

$$SPS = 0.85$$

3. Randomization and Blinding (RB): Double-blind and quadruple-masked, this approach minimizes biases effectively.

$$RB = 0.9$$

4. Control Group Appropriateness (CGA): A well-matched placebo control group ensures unbiased comparison, increasing trial validity.

$$CGA = 0.8$$

5. Patient Population Relevance (PPR): Involving mild-to-moderate Alzheimer's cases aged 50–87 with stable background medication ensures applicability to real-world cases.

$$PPR = 0.85$$

6. Compliance and Dropout Management (CDM): Monthly assessments and safety monitoring protocols help retain participants and track adherence.

$$CDM = 0.8$$

7. Regulatory Compliance (RC): The study adheres to FDA guidelines and has a Data Safety Monitoring Board (DSMB) overseeing safety.

$$RC = 0.95$$

8. Safety Monitoring (SM): Comprehensive monitoring of vital signs and adverse events maintains high safety standards.

$$SM = 0.9$$

9. Follow-Up Duration (FD): A 52-week period allows sufficient observation of drug effects on Alzheimer's progression.

$$FD = 0.9$$

Calculation of P(P3D)

The probability P(P3D) is calculated by averaging these factor scores:

$$P(P3D) = \frac{PER + SPS + RB + CGA + PPR + CDM + RC + SM + FD}{9}$$

$$P(P3D) = \frac{0.9 + 0.85 + 0.9 + 0.8 + 0.85 + 0.8 + 0.95 + 0.9 + 0.9}{9} = 0.865$$

$$P(P3D) = 86.5\%$$

The calculated probability P(P3D) of 0.865, or 86.5%, suggests that the design of Simufilam's Phase III trial is highly likely to support demonstrating the drug's efficacy in AD if there any efficacity. This non-conditional probability assessment clarifies how each design factor

independently contributes to the trial's overall success potential, providing a realistic evaluation without interdependent assumptions.

The Final Probability

To complete this probability analysis of Simufilam's likelihood of success in Phase III trials, we multiply the probabilities calculated for each factor to yield an overall probability of success, denoted as

$$P(S) = P(T) * P(D) * P(PS3) * P(P3D)$$

Substituting the values from our analysis:

$$P(S) = 0.000162 * 0.44 * 0.0519 * 0.865$$

$$P(S) = 0.0000032 = 0.00032\%$$

This final probability of *0.00032%* underscores the extreme unlikelihood of Simufilam achieving success in its Phase III trials, based on the combination of conditional and independent assessments across multiple critical factors. Each factor has a substantial influence on the final outcome, and the cumulative analysis provides a rigorous, transparent, and data-driven projection of Simufilam's potential, one that aligns with both empirical evidence and statistical rigor.
In conclusion, the probability of Simufilam's success is extraordinarily low, reinforcing our hypothesis about its efficacy. This probabilistic approach serves as a dependable framework, incorporating scientific rigor and clarity, for evaluating the drug's potential in Alzheimer's disease treatment.

We will now develop a verification model to reinforce the accuracy of our findings. By following this process, we will reach a probability estimate of Simufilam's likely success or failure, framed within a rigorous mathematical structure.

Disclaimer: This paper discusses our analysis of SAVA. It is important to disclose that we have a financial interest in this matter, as we will profit if the stock price declines.

Probability of Simufilam's Efficacy in Alzheimer's Disease:

As we evaluate the therapeutic potential of Simufilam, a prospective treatment for AD developed by Cassava Sciences, we find several critical challenges that sharply reduce the likelihood of clinical success. Given that Cassava's valuation is heavily contingent on Simufilam's performance, the probability of therapeutic efficacy (P_eff) directly informs our investment thesis. In this analysis, we outline the core factors affecting Simufilam's efficacy, building a comprehensive probabilistic model that integrates pharmacokinetic limitations, biochemical interactions, and historical efficacy data for similar drugs. Using both published literature and pharmacodynamic standards, we assign probability weights to these critical factors, ultimately calculating a Probability of Efficacy (P_eff) for Simufilam in Alzheimer's treatment as *0.003375%.* This outcome supports a high-confidence short position on Cassava Sciences, reflecting severe overvaluation based on the drug's speculative success.

Building the Probability Model

The probability of Simufilam's efficacy is modeled by analyzing several factors critical to AD treatment, each affecting the drug's likelihood of success:

1. Blood-Brain Barrier Penetration (BBB_P)
2. Target Specificity (T_S)
3. Efficacy on Aβ Pathology (Aβ_E)
4. Tau Pathology Factor (Tau_P)
5. Synaptic Integrity (Syn_I)
6. Neuroinflammation Factor (N_I)
7. Historical Efficacy of α7nAChR Targeting (α7nAChR_H)

Each component is assigned a probability value between *0* and *1*, reflecting its positive impact on Simufilam's potential efficacy.

1. Blood-Brain Barrier Penetration (BBB_P)

BBB penetration is essential for any drug targeting the central nervous system (CNS). Simufilam's LogP value of 1.1 and a half-life of 4.5 hours indicate a significant limitation in its BBB penetration capability. For optimal BBB penetration, an AD drug typically has a LogP between 2 and 3, with other pharmacokinetic factors supporting prolonged CNS presence. Given these factors:

$$BBB_P = 0.75$$

2. Target Specificity (T_S)

Simufilam's target, FLNA, is widely expressed across various tissues, raising concerns about specificity. Off-target effects and interactions with non-AD pathways reduce the drug's specificity, which is crucial in achieving targeted AD pathology modification. Assigning weight:

$$T_S = 0.25$$

3. Efficacy on Aβ Pathology (Aβ_E)

Simufilam targets the neurotoxic effects of Aβ42 by interacting with FLNA and α7nAChR. However, it lacks any direct mechanism to clear amyloid plaques or oligomers, which are fundamental drivers of AD pathology. This deficiency is critical given the multifactorial nature of Aβ42 toxicity, including plaque buildup and protein interactions that Simufilam does not address.

$$\text{Aβ\_E} = 0.15$$

4 Tau Pathology Factor (Tau_P)

Tau hyperphosphorylation and the resulting formation of neurofibrillary tangles (NFTs) are key contributors to AD. Simufilam's mechanism does not interact with kinases or other enzymes involved in tau hyperphosphorylation, nor does it reduce tau aggregation.

Tau pathology weight:

$$\text{Tau\_P} = 0.05$$

5. Synaptic Integrity (Syn_I)

Partial stabilization of FLNA may offer some synaptic support. However, without direct action on Aβ oligomer toxicity, which disrupts synaptic signaling, Simufilam is unlikely to maintain synaptic integrity effectively.

Estimated probability:

$$\text{Syn\_I} = 0.3$$

6. Neuroinflammation Factor (N_I)

Chronic neuroinflammation is associated with Aβ plaque accumulation, contributing to cognitive decline in AD. Simufilam does not address pro-inflammatory cytokines or other neuroinflammatory pathways.

Assigning:

$$\text{N\_I} = 0.2$$

7. Historical Efficacy of α7nAChR Targeting (α7nAChR_H)

Historically, drugs targeting α7 nicotinic acetylcholine receptors (nAChR) have failed to deliver clinical efficacy in AD trials, despite a favorable safety profile. This factor reflects the limited clinical potential of drugs centered on α7nAChR interactions.

$$\text{a7nAChR\_H} = 0.1$$

Probability Equation Construction and Calculation

The total probability of efficacy (P_eff) is derived by multiplying each of the probability factors, as shown in the formula below:

$$Peff = BBB_P * T_s * A\beta_E * Tau_P * Syn_I * N\_I * a7nAChR\_H$$

Substitute the assigned values for each factor:

$$Peff = 0.75 * 0.25 * 0.15 * 0.05 * 0.3 * 0.2 * 0.1$$

$$Peff = 0.00003375 = 0.003375\%$$

This equates to *a 0.003375%* probability of Simufilam achieving clinical efficacy in treating AD.

Final Probability

We estimate a POS for Simufilam in its Phase III trials to be between 0.00032% and 0.0034%, indicating a high statistical likelihood of failure. While these numbers may support a strategy of shorting the stock, it's important to acknowledge the inherent unpredictability in drug development, which can sometimes defy statistical odds. Top of Form

Non-Scientific Reasons Why We Are Shorting Cassava Sciences

In the second part of this paper, we shift our focus from the scientific basis of Cassava Sciences' drug Simufilam to the numerous allegations and legal controversies surrounding the company. We believe it is essential to examine the various claims of misconduct, data manipulation, and questionable practices that have surfaced. These allegations paint a troubling picture of a company under siege from numerous fronts, and while the scientific side of Cassava's drug development has raised significant concerns, the allegations surrounding the company further reinforce our beliefs. The decision to short Cassava Sciences' stock can be solidified by several non-scientific concerns surrounding the company. Comprising of its clinical trials, and its management's conduct.

Disclaimer: This paper discusses our analysis of SAVA. It is important to disclose that we have a financial interest in this matter, as we will profit if the stock price declines.

This section aims to expand on the unethical and dubious activities involving compensation schemes, questionable personnel overseeing trials, and the broader manipulation of trial data – reported by the SEC in part. All these factors contribute to the rationale to take a short position on the stock, highlighting the company's inability to sustain its current value.

1.FLNA: A Target Nobody Believes In

One of the clearest indicators that Simufilam is built on questionable scientific ground is the limited interest in FLNA as a therapeutic target for AD (*FLNA Alzheimer - Search Results - PubMed*, 2024). If FLNA were a blockbuster therapeutic target for the treatment of AD, it would have garnered far more attention from the scientific community. However, to date, Cassava Sciences is all but the only biotech to test this hypothesis. Since FLNA was first proposed as a target for AD in 2012, only 14 research articles have been published on it, and this, despite over a decade of research in the field (*FLNA Alzheimer - Search Results - PubMed*, 2024). Notably, six of these publications are authored by Dr. Hoau-Yan Wang, the lead researcher of Cassava Sciences.

To provide context, between 2012 and 2024 (present day), 48,998 papers have been published on *amyloid and Alzheimer's disease* (Amyloid Alzheimer - Search Results - PubMed, 2024). Amyloid is one of the most extensively studied targets in the field. Additionally, tau protein has also been a significant focus of AD research, having 22,216 papers published during the same period (Tau Alzheimer - Search Results - PubMed, 2024). Meanwhile microglia - an emerging target for AD that has spiked interest in the field in recent years - have been the subject of 7,042 scientific publications during the same time period (*Microglia Alzheimer - Search Results - PubMed*, 2024). These numbers illustrate that the scientific community is actively investigating multiple pathways in the effort to find a cure for AD. Still, research related to *FLNA and AD* represents only 14 studies over the same time period, with 6 of them made by Dr. Wang. This stark disparity suggests that the scientific community does not consider FLNA to be a promising target for AD research.

The limited amount of research on FLNA is not accidental; it reflects a lack of confidence from both the scientific and pharmaceutical communities. AD represents a significant global health crisis, with the U.S. alone spending $321 billion on AD-related care in 2022, a figure projected to exceed $1 trillion by 2050 (PharmD, 2022). Any company that successfully develops an effective treatment for AD stands to gain substantial financial returns. Major pharmaceutical companies such as Eli Lilly, Biogen, and Roche have invested billions of dollars in the research of amyloid, tau, and microglia (Cummings et al., 2021). If FLNA were a credible target for treating AD, these companies would have pursued it. The fact that no pharmaceutical companies have explored FLNA as a sole target, indicates that it is not considered a viable approach to cure AD.

Dr. Wang first focused on Remoxy – a drug aimed at opioid overdose – that unfortunately failed to deliver positive results. One year later, Dr. Wang shifted his focus on AD, bringing with him his (Naloxone) theory that FLNA could be a therapeutic pathway. Despite the vast differences in pathophysiology of these conditions – AD vs. Opioid overdose. This sudden change raises additional questions to the long list of existing inquiries, raising doubts on the scientific basis of FLNA as a target for AD - see section *4, Naloxone Binding to FLNA and the VAKGL Peptide*.

If FLNA represented a genuine breakthrough in AD research. It is unclear why, over the course of a decade, no other researchers or institutions, aside from Dr. Wang and Cassava Sciences, have pursued FLNA as a target. The lack of attention from the scientific community suggests that FLNA is unlikely to play a significant role in the progression of AD or in the development of effective treatments.

In conclusion, Cassava Sciences is promoting a hypothesis that lacks support from the scientific community. Given the critical importance of AD and the substantial financial and scientific resources dedicated to finding a cure, if FLNA were a legitimate target, it would likely have attracted widespread interest and research efforts (*Investing in Alzheimer's Research*, 2024) (Cummings et al., 2021). The absence of such interest strongly indicates that FLNA has little relevance to Alzheimer's.

2. All The Retracted Papers of Dr. Wang

Dr. Hoau-Yan Wang's research, which forms the foundation of Cassava Sciences' experimental AD drug - Simufilam - has been associated with several retractions and expressions of concern. These issues raise important questions about the reliability of the research underpinning Simufilam's development. Given Wang's history of data-related issues, it is essential to critically assess the scientific validity of Simufilam's MOA.

The Fragile Foundation of Simufilam's Mechanism

Simufilam is based on the hypothesis that altered forms of FLNA contribute to the pathophysiology of AD, and that correcting these alterations could mitigate disease progression. This hypothesis is largely derived from Dr. Wang's earlier studies, which are now the subject of considerable scrutiny. The validity of Simufilam's development must be evaluated considering these concerns, particularly given the critical role that these studies play in supporting the drug's proposed mechanism - which led to more than $16 million of NIH grants (Wosen, 2024), (Walker, 2024).

Retractions and Expressions of Concern

Retractions in scientific literature often indicate significant issues related to data integrity or methodological errors. Several of Wang's studies have been retracted or are under investigation, particularly those that form the basis of the FLNA hypothesis.

1. **2008 Study: High-Affinity Naloxone Binding to FLNA**
   One of the earliest studies by Wang that relates to his FLNA hypothesis was retracted, due to evidence of data manipulation (Wang & Burns, 2009). The study claimed that naloxone binds FLNA with high affinity. However, irregularities in the Western blot data—including obvious splicing—led to the paper's retraction. Wang defended the data, attributing the issues to image compression artifacts, but was unable to provide the raw data necessary to substantiate his claims. This retraction is particularly significant as it casts doubt on the very foundation of Simufilam's MOA (Retraction Note, 2022).

Disclaimer: This paper discusses our analysis of SAVA. It is important to disclose that we have a financial interest in this matter, as we will profit if the stock price declines.

1. **2009 Study: Naloxone's Pentapeptide Binding Site on FLNA**

   Following the 2008 paper, Wang published another study further detailing naloxone's interaction with FLNA (Wang & Burns, 2009). This paper faced similar issues, with multiple figures showing signs of manipulation, such as missing controls and suspicious splice lines. Once again, Dr. Wang claimed that technical errors, including scanner malfunctions, were responsible for the inconsistencies. Despite these excuses, the journal editors retracted the paper due to the overwhelming evidence of data tampering. This marks a second major strike against the research supporting Simufilam, further eroding confidence in its underlying science (Retraction Note, 2022).

2. **Dissociating β-Amyloid from α7 Nicotinic Acetylcholine Receptor by a Novel Therapeutic Agent, S 24795, Normalizes α7 Nicotinic Acetylcholine and NMDA Receptor Function in Alzheimer's Disease Brain**

   In 2009, a study examined interaction between β-amyloid peptides and the α7 nicotinic acetylcholine receptor (Wang et al., 2009). The study concluded that β-amyloid binds to α7nAChR on neurons, leading to synaptic dysfunction—a salient feature in the pathology of Alzheimer's. Though the findings were influential at the time, eventually questions of integrity in the data arose. Similar to other studies in this field, some of the figures showed unusual inconsistencies: there were unexplained splice junctions; proper controls were missing. The authors blamed technical mishaps for these issues, but even with these explanations, scientific scrutiny did not let up. Later studies, including a 2022 follow-up study in the same journal, questioned the reproducibility of these findings and further dented any confidence in the proposed mechanism. (Expression of Concern, 2022)

3. **S 24795 Limits β-Amyloid–α7 Nicotinic Receptor Interaction and Reduces Alzheimer's Disease-Like Pathologies**

   In November 2009, Wang published a study on the effects of S 24795 in limiting the interaction between β-amyloid and the α7 nicotinic receptor and proposed that the compound could reduce Alzheimer's disease-like pathology (Wang et al., 2009). The majority of this research has since been called into question. Concerns were raised about potential manipulation of Western blot data, casting doubt on the study's integrity. In

response, the journal issued an Expression of Concern in 2023, noting that the academic authorities at the City University of New York (CUNY) were investigating these allegations. Pending the outcome of this inquiry, confidence in the study's findings has been significantly compromised, adding to the broader skepticism surrounding research in this area.

4. **2012: Reducing Amyloid-Related Alzheimer's Disease Pathogenesis by a Small Molecule Targeting Filamin A**

   Perhaps most damaging to Cassava Sciences is the ongoing investigation into Dr. Wang's 2012 study on FLNA and Aβ, published in *The Journal of Neuroscience* (Wang et al., 2012). This study is directly related to Simufilam and claims that targeting FLNA could reduce amyloid beta-related neurodegeneration, a hallmark of AD. However, the journal has since issued an expression of concern due to irregularities in the Western blot images, once again hinting at possible data manipulation. While the investigation remains open, the cloud of uncertainty surrounding this pivotal research is grave enough to warrant serious concern about Simufilam's legitimacy (Expression of Concern, 2022).

5. **Simufilam suppresses overactive mTOR and restores its sensitivity to insulin in Alzheimer's disease patient lymphocytes**

   In yet another blow to Dr Wang and Cassava Sciences, an expression of concern has been issued regarding a 2023 study led by Dr. Wang, published in *Frontiers in Aging* (Wang et al., 2023). This study claims that Simufilam can suppress overactive mTOR and restore its sensitivity to insulin in lymphocytes from AD patients—an important finding given mTOR's role in cellular aging and disease progression. However, *Frontiers* has raised concerns over the integrity of the images used in the paper, casting further doubt on the validity of the results. The investigation, still ongoing, follows the Committee on Publication Ethics (COPE) guidelines. This additional layer of uncertainty surrounding Simufilam's supposed mechanisms deepens the skepticism around the drug's potential, as unresolved image irregularities may suggest more data manipulation.

Broader Pattern of Fraud in Dr. Wang's Research

Dr. Wang's research history shows a broader pattern of data-related concerns extending beyond AD. For example, his studies on prenatal cocaine exposure, published in 2009 and 2014, were retracted due to similar issues, with Western blot images (Bakshi et al., 2011) (Bakshi et al., 2014). These recurring problems suggest a systemic issues with data integrity across multiple areas of Dr. Wang's research (Retraction Note) (Retraction Note).

The Rarity of Retractions and Dr. Wang's Defiance

Scientific retractions are exceedingly rare. A 2012 study found that only about 0.0082% of published papers are retracted (Fang et al., 2012). For most researchers, a single retraction can be a career-damaging event, yet Dr. Wang has faced multiple retractions. This pattern suggests something far more troubling than isolated mistakes, as it points to a consistent scientific misconduct from Dr. Wang.

Despite the mounting evidence against him, Dr. Wang continues to deny any wrongdoing, asserting that his data and conclusions are valid (Piller, 2023). His repeated defense of manipulated data—even in the face of overwhelming evidence—raises serious questions.

Key Takeaways: A Drug Built on Dubious Grounds

The scientific foundation of Simufilam is heavily reliant on studies that have been retracted or that are under investigation. While Cassava Sciences has positioned Simufilam as a potential breakthrough in AD treatment, the data integrity concerns surrounding Dr. Wang's research raise significant questions regarding the reliability of the development of Simufilam. Further investigations are necessary to clarify the validity of the FLNA hypothesis and Simufilam's efficacy.

3. DOJ vs Dr Wang

In June 2024, Dr. Hoau-Yan Wang, was indicted for defrauding the U.S. National Institutes of Health (NIH) of approximately $16 million in federal grant funds (NIH). The DOJ alleges that

Wang fabricated and falsified data in NIH grant applications to secure funding between 2017 and 2021 (DOJ, 2024) .

> "As alleged, the fraudulent grant applications to the NIH sought funding for scientific research of a potential treatment and diagnostic test for Alzheimer's disease and resulted in the award of approximately $16 million in grants from approximately 2017 to 2021, part of which funded Wang's laboratory work and salary." (DOJ, 2024).

Those data were central to the development of Simufilam. Without these NIH funds, which supported the early preclinical and clinical work, Simufilam would probably not have advanced to clinical trials.

The charges against Wang call into question the legitimacy of Simufilam itself. The drug, based on the controversial hypothesis that it targets altered forms of FLNA to disrupt harmful AD processes, advanced to Phase III trials partly due to Wang's allegedly manipulated research.

Wang now faces charges with "one count of major fraud against the United States, two counts of wire fraud, and one count of false statements. If convicted, he faces a maximum penalty of 10 years in prison for the count of major fraud, 20 years in prison for each count of wire fraud, and five years in prison for the count of false statements." (DOJ, 2024).

4. SEC vs Dr Wang

The Security and Exchange Commission (SEC) has initiated cease-and-desist proceedings against Dr. Hoau-Yan Wang, citing concerns of public interest under Section 8A of the Securities Act of 1933 and Section 21C of the Securities Exchange Act of 1934. The SEC's investigation highlights serious allegations related to the manipulation of biomarker results from Cassava Sciences' Phase 2b clinical trial of PTI-125 (Simufilam). According to the findings, Dr. Wang, who was responsible for analyzing cerebrospinal fluid (CSF) samples from the trial, unblinded himself to a portion of the patients before conducting his analysis. This action allowed him to selectively adjust the data, ultimately presenting significant improvements in AD biomarkers for patients receiving

Simufilam (PTI-125), compared to the placebo group. These potential manipulated results formed the basis of Cassava Sciences' claims regarding Simufilam's effectiveness in treating AD. These claims played a pivotal role in influencing investor sentiment and boosting the company's stock price.

Dr. Wang's role in the manipulation of the data is central to the SEC's case. The clinical trial was supposed to be conducted under blind conditions - meaning neither the patients nor the personnel should have known who was receiving what. Blind clinical trials are a standard practice to eliminate bias in clinical trials. However, Dr. Wang unblinded himself to 23 of the 64 patients in the trial, this allowed him to alter the biomarker data in favor of his treatment – making the data appear more conclusive that it really was. This breach of protocol directly undermines the integrity of the trial results (SEC vs Wang).

The manipulation occurred during two different phases of biomarker testing - referred to as Round 1 and Round 2. In the first round, Cassava contracted a European laboratory to analyze most of the biomarkers, while Dr. Wang handled two additional biomarkers. The Round 1 results were completed in early 2020, it showed no meaningful difference between the placebo and treatment groups - which failed to replicate the promising results from an earlier Phase IIa trial. Despite these underwhelming findings, Dr. Wang was instructed to reanalyze the data in Round 2. Before this second round of analysis, he had already unblinded certain patients, giving him the opportunity to skew the data in favor of Simufilam. The manipulation of Round 2 resulted in a favorable evaluation regarding Simufilam's efficacy, demonstrating that patients in the treatment arms had statistically significant improvements in multiple biomarkers compared to the placebo group – acknowledging a grave data manipulation that completely misleads the data from this Round 2.

Cassava Sciences' public dissemination of these manipulated results had a profound impact on the company's stock. On September 14, 2020, the company issued a press release stating that patients treated with Simufilam showed statistically significant improvements in biomarkers of Alzheimer's pathology, neuroinflammation, and neurodegeneration compared to placebo patients. Cassava Sciences further asserted that the bioanalyses were conducted under blind conditions - which was proven to be false as previously explained. Following this announcement, the

company's stock more than doubled, rising from *$3.40* to *$8.41* per share, driven by the seemingly positive trial data. Investors were misled into believing that Simufilam was an effective treatment for AD – not knowing that it was all based on fraudulent data.

Cassava Sciences capitalized on their stock price's surge by raising substantial capital. In November 2020, the company sold over 9 million shares, raising approximately $70 million (SAVA 8K, 2020). Then, in February 2021, Cassava filed a new registration statement, netting over $190 million (SAVA 8K, 2021). These capital raises were made possible only because of the manipulated Phase IIb data. Without this fraudulent data, Cassava Sciences would not have been able to secure the funding necessary to advance to Phase III trials, as investors would not have backed the company based on the true trial results. In essence, the company's ability to move forward with Phase III trials is directly tied to the deception that inflated both their stock price and their access to capital.

In addition to all that, Dr. Wang's personal financial interests also came into play. In addition to his role as a scientific advisor and consultant for Cassava Sciences, he owned 18,571 Cassava stock and unexercised options at a weight average price of $4.22. He also stood to benefit from Cassava Sciences *Cash Incentive Plan*, which provided cash payments based on meeting certain valuation benchmarks. This financial incentive adds another layer to the conflict of interest in his actions, as he directly profited from the stock price increase - driven by his manipulated data.

The SEC accuses Dr. Wang of violating several key securities laws, including *Section 17(a)* of the *Securities Act and Section 10(b)* of the *Exchange Act*, as well as *Rule 10b-5*. These provisions prohibit fraudulent practices in the offer or sale of securities, and the SEC argues that Dr. Wang's manipulation of the biomarker data constituted a clear violation of these laws.

As a result of the SEC's investigation, Dr. Wang has been ordered to cease and desist from further violations of securities laws, and to pay civil penalties totaling $50,000. These penalties will be paid in installments over the course of a year, and a *Fair Fund* has been established to distribute the penalties to affected investors. The SEC's findings also pave the way for potential private

lawsuits from investors who were harmed by the manipulated data and the subsequent stock price inflation.

The implications for Cassava Sciences are severe. The SEC's findings undermine the credibility of the entire clinical trial process for Simufilam and raise serious doubts about the drug's efficacy. For us, these developments provide empirical evidence supporting our thesis that the company's stock is overvalued and based on fraudulent information. As the case unfolds, Cassava Sciences faces significant legal, financial, and reputational risks - which are likely to impact its stock price and ability to raise additional capital.

5. SEC vs Cassava Sciences

In September 2024, the SEC launched a lawsuit against Cassava Sciences, Inc., its founder and former CEO Remi Barbier, and Dr. Lindsay Burns, the former Senior Vice President of Neuroscience (Case No. 24-cv-1150). This legal action revolves around misleading claims about the results of Cassava's Phase IIb clinical trials for their AD treatment candidate, PTI-125 (also known as Simufilam). According to the SEC, Cassava's Phase IIb results were misleading in five ways, all of which had a substantial impact on investors and the company's financial success.

At the center of the case is the manipulation of clinical trial data. Cassava had claimed that the biomarker analysis in their Phase IIb trial was conducted under strict, blinded conditions, which are essential in eliminating bias. However, the SEC's investigation revealed that Dr. Wang, the co-inventor of Simufilam, was able to partially unblind himself to the data due to information negligently provided by Dr. Burns. This partial unblinding compromised the integrity of the results since Dr. Wang had a financial and professional stake in Simufilam's success.

Furthermore, Cassava failed to disclose that Dr. Wang conducted a second round of biomarker testing after being partially unblinded. An internal audit later deemed his laboratory "unacceptable" and "temporarily not qualified" to conduct future biomarker analyses due to severe procedural failings (SEC vs SAVA, 2024). Despite these audit findings Cassava Sciences did not disclose to investors at the time, until they had secured significant investment based on the

fraudulent results of the Phase IIb trial. Instead, the company continued to work with Dr. Wang until mid-2024 and misrepresented the integrity of its data to secure significant investments. By failing to disclose these conflicts of interest and procedural lapses, Cassava Sciences violated multiple securities laws - as detailed in the SEC complaint.

One of the most troubling aspects of the trial was the manipulation of cognition data. Cassava selectively removed 40% of the study participants from its analysis, resulting in a more favorable presentation of Simufilam's effects on episodic memory. Dr. Burns, who was unblinded to the data, removed both high- and low-performing patients, skewing the results to suggest a cognitive improvement in patients treated with Simufilam. This form of post-hoc analysis, which was not part of the original clinical trial protocol, gave the appearance of efficacy where none existed. Crucially, this manipulation was not disclosed to investors at the time. It wasn't until July 2024—after Cassava had raised hundreds of millions of dollars based on these misrepresented results—that the company finally admitted to excluding a significant portion of the dataset from its analysis (SEC vs SAVA, 2024).

For instance, when the full dataset is considered, the changes in episodic memory errors between the placebo and treatment groups were negligible. The placebo group saw a change of -3.4 points, while the group receiving 50mg of Simufilam only improved by -2.8 points, and the 100mg group showed no change. These results clearly contradict Cassava's public claims of significant cognitive improvements, underscoring the unethical nature of the data manipulation (SEC VS SAVA).

	Placebo	50mg	100mg
Phase 2b NCT04079803	-1.5	-5.7	-4.5
Real Result According to the SEC	-3.4	-2.8	-0.1

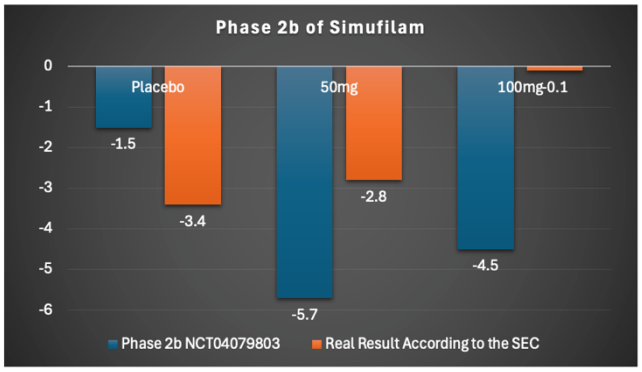

Figure 8. Excel Model comparing the results of the SEC for the Phase IIb of Simufilam and the results Cassava Sciences gives for its Phase IIb (SEC vs Cassava, 2024) (NCT04079803)

Cassava leveraged these misleading Phase IIb results to raise substantial capital. After publicizing their Phase IIb outcomes in September 2020, the company's stock price more than doubled, and they raised approximately $70 million in November 2020 and another $190 million in early 2021. These capital raises were based largely on the false perception that Simufilam was showing promise as an AD treatment.

The SEC alleges that without these fraudulent claims, it would have been difficult, if not impossible, for Cassava to secure the necessary funds to continue with its Phase III trials. Several financial institutions indicated that the company's ability to raise capital hinged on the success of the Phase IIb trial. Therefore, the manipulation of data not only misled investors but also became integral to Cassava's financial survival.

Simufilam represents Cassava's only significant asset, and the company's future revenue prospects are entirely dependent on its success. The SEC's revelations have severely discredited the scientific basis for Simufilam, calling into question whether it will ever receive FDA approval. Additionally, the ongoing legal challenges and loss of investor trust have cast doubt on Cassava's ability to raise future capital.

As a result of the SEC's investigation, Cassava Sciences, Inc., along with Remi Barbier and Lindsay Burns, agreed to settle the civil charges by paying $40 million, $175,000, and $85,000, respectively, to resolve the charges brought by the SEC (Reuters, 2024).

6. The CUNY Investigation

The findings from the CUNY investigation into Dr. Hoau-Yan Wang's laboratory at The City College of New York (CCNY) provide substantial evidence relevant to our short position on Cassava Sciences. The investigation, conducted by CUNY, identified numerous scientific and procedural deficiencies in the bioanalytical studies that underpin Cassava's clinical claims regarding Simufilam's efficacy. These findings directly question the credibility of the science supporting Simufilam, raising red flags about Cassava's valuation and the prospects of the drug's success.

One of the critical findings in the CUNY investigation was the lack of validation for the ELISA assays used to measure crucial biomarkers in cerebrospinal fluid (CSF) samples. These biomarkers were vital to Cassava's claims that Simufilam positively affects cognitive function by modulating proteins implicated in AD. However, CUNY found that Dr. Wang's lab failed to conduct in-house validation of the assays for parameters such as accuracy, precision, and sensitivity. Instead, the lab relied on commercially available ELISA kits without verifying their performance for the specific experimental conditions of Cassava's studies. This omission of assay validation is a fundamental breach of scientific standards, as validated assays are necessary to ensure data reliability. Without this validation, the study data used to support Simufilam's purported benefits become speculative and unreliable, undermining the credibility of any conclusions about the drug's efficacy.
Additionally, CUNY found significant issues with the processing stage of the ELISA assays. The investigation revealed that the lab used a linear regression model to interpret calibration data, despite a clear non-linear relationship between the biomarker concentrations and the assay responses. Dr. Wang himself admitted to being unaware of alternative curve-fitting models available within the software used. This oversight is significant, as the incorrect statistical model would yield inaccurate biomarker measurements, further compromising the validity of the conclusions drawn. This use of an inappropriate model to interpret biomarker data questions the accuracy of Simufilam's reported effects and adds to the concerns about Cassava's clinical program.

Record-keeping and documentation deficiencies were another severe issue uncovered in the CUNY investigation. Dr. Wang's lab failed to maintain essential records, such as documentation

of sample storage, tracking, calibration standards, and experimental protocols, making it impossible to verify or replicate key aspects of the studies. Furthermore, the lab did not maintain source records for Western blot analyses, nor did it keep audit trails for the equipment used in the ELISA assays. This lack of rigorous documentation is a fundamental flaw, as reliable scientific research relies on meticulous record-keeping to ensure data integrity, reproducibility, and transparency. The absence of these records significantly undermines the trustworthiness of the data supporting Simufilam's clinical program, raising significant concerns for investors.

CUNY's findings also revealed troubling practices in data handling, specifically the arbitrary exclusion of data points from triplicate analyses. In numerous cases, the lab excluded one of three data points when calculating mean biomarker concentrations without consistent criteria for identifying outliers. This practice of data exclusion, without a standardized or transparent rationale, is a serious breach of scientific integrity. When questioned, Dr. Wang acknowledged that these exclusions were due to mistakes in formula application rather than any systematic approach. Such selective data manipulation is highly concerning, as it introduces the possibility that the data was shaped to produce a favorable outcome for Simufilam. This finding further weakens the credibility of the data and raises additional concerns about the reliability of Cassava's clinical claims.

A further significant deficiency noted in the CUNY report was the absence of quality control (QC) samples in the ELISA assays. QC samples are essential in bioanalytical studies to verify that assays are performing consistently and accurately over time. Dr. Wang admitted that no QC samples were included in the study, meaning that there was no ongoing verification to ensure the assay's reliability. The lack of QC samples introduces considerable uncertainty in the data, as there is no benchmark to confirm that the assays yielded consistent results. This omission fundamentally undermines the reliability of the biomarker data presented, which is critical to Cassava's claims about Simufilam's efficacy.

Another crucial issue was highlighted by the CUNY investigation, the failure to assess the stability of the CSF and blood samples used in the study. Stability testing is crucial for ensuring that biomarker levels remain consistent over time, particularly when working with biological samples that may degrade under certain conditions. Dr. Wang acknowledged that his lab did not conduct

any stability assessments to confirm that the samples remained viable throughout the storage and handling processes. This failure introduces significant doubt about the reported biomarker levels, as it is unclear whether the measurements reflect actual biological conditions or are artifacts of sample degradation.

Finally, CUNY's inspection revealed serious lapses in equipment maintenance and data security within Dr. Wang's lab. Key pieces of equipment, including the ELISA plate reader and the freezers used to store biological samples, had not been calibrated for years. Furthermore, the lab's computers lacked access controls, meaning that any personnel could access and potentially alter data without leaving a trace. These operational deficiencies introduce additional risks of measurement errors and potential data tampering, further undermining the credibility of the data used to support Simufilam's clinical claims.

In conclusion, the CUNY investigation presents a comprehensive account of scientific malpractice and procedural failures that significantly weaken Cassava Sciences' claims about Simufilam. The lack of assay validation, the misapplication of statistical models, the failure to maintain proper documentation, and the absence of quality control all point to data that may be unreliable or manipulated. The findings from CUNY's report provide strong factual support for our position on Cassava Sciences, underscoring concerns about the integrity of the clinical data underpinning Simufilam's development.

7. QCM Report

The Quintessential Capital Management (QCM) report on Cassava Sciences intensifies our belief that Cassava is a short position, reinforcing doubts around the legitimacy of its Alzheimer's drug, Simufilam. QCM's investigative findings highlight deeply concerning issues within Cassava's clinical trials and raise serious questions about the integrity and intent of its management. This

report provides a meticulous review of Cassava's corporate behavior, from perverse financial incentives to manipulation in clinical trial conduct, all of which create a compelling case for shorting the stock.

Incentive Compensation and Executive Greed

Cassava Sciences' executive compensation structure presents serious conflicts of interest. As outlined in Quintessential Capital Management's (QCM) report, the company's incentive structure appears to encourage management to focus on short-term stock price increases, with no regard to long-term success or actual drug development milestones. The executive team, led by CEO Remi Barbier, has structured compensation in such a way that bonuses are awarded not based on clinical progress or FDA approval but merely on short-term stock price appreciation.

This compensation scheme is designed around market capitalization milestones, ranging from $200 million to $5 billion (QCM Report); (*SAVA 8K 2020 Bonus Plan*, 2020), with management pocketing tens of millions of dollars each time the stock hits a specific price target. The scheme rewards management with bonuses of up to $50 million at the highest level, regardless of whether the drug candidate, Simufilam, succeeds or fails.

> "Moreover, Cassava's management has somehow managed to approve what looks to us like an outrageous. compensation system, literally rewarding short-term stock price fluctuations regardless of more traditional metrics as [sic] such as profitability or drug approval milestones.
>
> The plan rewards management if Cassava's stock reaches certain market capitalization thresholds and holds them for a period of only 20 days. Bonuses range from $10m to $50m per threshold and the thresholds range from $200m to $5bn. Intermediate amounts, unsurprisingly have not been disclosed, but we estimate the total bonus pool to be around $450m. Clearly management would get rich temporarily inflating Cassava's stock price by creating unlikely expectations for the prospect of its only drug, Simufilam. Should the drug then fail to deliver, and we think it will, shareholders will be wiped out, but management will get to keep their large bonuses." (QCM Report).

Such a structure creates an environment ripe for stock price manipulation. If the executive team is incentivized solely by the stock's performance over short periods, it has every reason to inflate expectations and drive the price upward through marketing and misleading claims. As QCM suggests, this could explain why Cassava's stock surged by over 1,000% at the height of public hype, despite the lack of any proven efficacy for Simufilam.

The incentive to pump up the stock price creates a classic 'pump and dump' scenario (QCM Report). Management, enriched by stock options and bonuses, could profit from the inflated stock price before the inevitable collapse, leaving shareholders and patients devastated when the drug ultimately fails to meet expectations. This behavior is not just unethical but also indicative of management prioritizing personal financial gain over corporate integrity and patient welfare.

Questionable Individuals Involved in the Clinical Trials

The integrity of Cassava Sciences' clinical trials is highly questionable due to the involvement of individuals with dubious credentials and criminal records. QCM's undercover investigation revealed significant red flags about the key personnel overseeing the trials.

One of the most concerning figures is Hilda, Cassava's Senior Clinical Research Associate (CRA), who was responsible for monitoring the Simufilam clinical trials. Hilda, according to QCM's report, has a criminal record that includes felony convictions for fraud and theft. Her appointment to such a crucial role raises severe concerns about the legitimacy of the trial oversight. A CRA is responsible for ensuring compliance with clinical protocols, protecting patient safety, and maintaining the scientific integrity of the data. Placing someone with a history of fraud in this position casts doubt on the reliability of the entire clinical trial process.

Moreover, QCM's investigation pointed out that Hilda may have been replaced by Cassava's Chief Medical Officer (CMO), Nadav Friedman, who himself has been involved in making allegedly fraudulent statements about the company's previous failed drug, Remoxy. Having a company

insider, particularly one with a history of securities fraud, oversee the trials exacerbates the already significant concerns over potential manipulation of trial results.

Additionally, one of the key clinical research centers involved in the Simufilam trials, IMIC Inc., is co-owned by Aimee Cabo, a figure with an even more colorful past. Cabo, who has claimed to be a nurse but is unlicensed, has a record of felony arrests for drug possession and a former career as a stripper and escort. This not only calls into question her credibility but also IMIC's suitability as a clinical research site. Cabo's involvement, along with her husband Boris Nikolov, whose own financial history raises suspicions of misconduct, undermines any confidence in the integrity of the data being generated by IMIC.

Furthermore, the Principal Investigator at IMIC, Evelyn Lopez-Brignoni, is a child and adolescent psychiatrist with no experience in neurodegenerative diseases similar to AD. She was also issued a rare FDA warning for failing to follow investigational protocols in a clinical trial, further highlighting the inadequacies in the clinical trial management.

Alleged Manipulation of Clinical Trials and Data

The alleged manipulation of Cassava Sciences' clinical trials adds another layer of concern. Beyond the scientific debate over Simufilam's efficacy, QCM's report raises alarming suspicions about how the trials were conducted, suggesting that the company may have distorted trial outcomes to present favorable results.

One of the key allegations is that Cassava allowed patients into the trials who likely did not have AD, effectively skewing the results. The inclusion criteria for the Simufilam trial were unusually broad, allowing for patients with possible or probable AD, rather than more stringent and definitive diagnoses. This opens the door to the inclusion of individuals who might simply have age-related memory loss or other forms of dementia, which could lead to better-than-expected results that do not reflect the drug's true efficacy for AD patients.

In one trial, Cassava allegedly excluded a significant number of patients—around 42%—from the final analysis, using highly dubious reasons such as patients answering too many or too few questions correctly. This suggests that the company may have been strategically excluding patients to inflate the perceived effectiveness of the drug. By removing patients with poor cognitive outcomes, Cassava could falsely present Simufilam as more effective than it truly is, leading to misleadingly positive results.

The lack of independent oversight further exacerbates these concerns. Cassava appears to have overseen the trials internally, with its own management monitoring the trials without any third-party verification. This raises serious questions about the credibility of the data, as it gives Cassava the ability to manipulate trial results without external scrutiny.

The Citizen Petition and Forensic Investigations

On August 18th, 2021, a Citizen Petition was filed with the FDA by Labaton Sucharow, a law firm specializing in SEC whistleblowing, which accused Cassava of forging its scientific data. The petition included forensic evidence of data manipulation, particularly in images and statistical anomalies used to support the efficacy claims for Simufilam (*Regulations.gov*, 2021).

The petition triggered a sharp decline in Cassava's stock price and brought the company's practices under intense scrutiny. Independent experts, including Dr. Elizabeth Bik, confirmed the allegations, pointing to specific examples where data appeared to be manipulated. Despite this, Cassava has refused to release the original data that could potentially refute these claims, raising suspicions that the data indeed was falsified (Press Release, 2021).

If these allegations are held, Cassava could be guilty of FDA fraud, violating both the False Claims Act and securities regulations. The company's failure to provide convincing rebuttals only strengthens the argument that its scientific research is fraudulent, further weakening its stock's value and long-term prospects.

Regulatory and Legal Exposure

Beyond the immediate financial risks posed to investors, Cassava faces significant regulatory and legal exposure. The QCM report outlines the potential for Cassava to face securities fraud charges, FDA fraud, and violations of the False Claims Act. These potential legal actions stem from the company's allegedly misleading statements about Simufilam's efficacy and the manipulation of clinical trial results.

Cassava's conduct has already prompted multiple investigations, including from the FDA, the SEC, and the Department of Justice. The involvement of these agencies suggests that the company's problems extend beyond typical biotech volatility and into the realm of criminal conduct. If Cassava is found guilty of securities fraud or any other regulatory violation, the financial penalties and reputational damage could be devastating, leading to the collapse of the company and a complete loss of shareholder value.

Moreover, Cassava's aggressive response to whistleblowers and critics further amplifies the risks. The company has engaged in intimidation tactics against those raising concerns, signaling that it may be attempting to silence dissent rather than address the underlying issues (Armstrong A., 2021).

Final Conclusion

After thoroughly evaluating both scientific and non-scientific factors, our POS estimate for Simufilam remains unchanged. In fact, these additional considerations reinforce our conviction that Simufilam will fail its Phase III trials by the end of the year. We estimate the POS for Simufilam in its Phase III trials to be between 0.00032% and 0.0034%, indicating a high statistical likelihood of failure. While these numbers may support a strategy of shorting the stock, it's

important to acknowledge the inherent unpredictability in drug development, which can sometimes defy statistical odds.

Knowing that the company is currently valued at a market cap of $1.39 billion, it's clear that this valuation hinges entirely on the potential success of Simufilam, its only asset. Once Simufilam inevitably fails its Phase III trials, expected by Q4 2024, the market will be forced to recognize that Cassava Sciences has no remaining value.

We anticipate that following Simufilam's failure, Cassava Sciences' stock will trade at or near its cash reserves. According to their *Q2 2024 10-Q filing*, the company reported *$207.3 million* in cash. However, factoring in the *$40 million* settlement with the SEC, we estimate their current cash position to be approximately *$167.3 million*. Additionally, in their *last press release*, Cassava Sciences projected a net cash use of *$80 to $90 million* for the second half of 2024, including the *$40 million* settlement. This would leave them with an estimated cash balance between *$117 and $127 million* by year-end.

Consequently, when computing the anticipated collapse, the company's valuation is likely to be restricted to its cash holdings, if not less, due to the inevitable mass sell-off. Based on these considerations, we predict that the share price will drop from *$28.98* to a range approximately *$3.49 to $1.94* - reflecting the market's recalibration to the company's cash value in the aftermath of Simufilam's failure.

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Disclaimer: This paper discusses our analysis of SAVA. It is important to disclose that we have a financial interest in this matter, as we will profit if the stock price declines.

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