On the Impossible:

Why Cassava Sciences' simufilam will fail Phase 3 clinical trials and the stock will trade to $2

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November 2024

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Executive Summary

In this work, I will **prove** that the simufilam Phase III trials will fail to meet their primary endpoints. I have done this before with Vital Therapies (Shkreli, 2015). While proving is much more difficult than hypothesizing, we occasionally can make a deterministic, definitive claim due to overwhelming circumstances which cannot be overcome.

The sole Cassava asset is **simufilam**, in development for Alzheimer's disease. The Phase III trial "RETHINK" is scheduled to report by the end of 2024. This trial will fail because simufilam does not work.

Simufilam has clearly shown its ineffectiveness in a Phase II trial where a controlled withdrawal study showed no statistical difference (not even close) between simufilam and placebo. A prior Phase II study was doctored by the company to appear as if it improved cognition, when—if anything—it did precisely the opposite. The person responsible for this was charged with fraud by the SEC.

The simufilam science is not viable. Simufilam was not designed to be a protein-protein interaction inhibitor, yet, this is the claim of Cassava. Protein-protein interaction inhibitors are some of the most complex types of drugs to design. Very few of them exist—and the ones that do—do not match simufilam's profile.

Simufilam, at best, has a 1uM affinity for its target. With poor pharmacokinetics and low brain partitioning, simufilam is doomed to work even if their hypothesis scientific hypothesis is sound.

The person responsible for their scientific hypothesis has been arrested by the FBI. Their hypothesis was absurd—that a protein, filamin A, has anything to do with Alzheimer's. The relationship between filamin A and amyloid-beta, in Cassava's telling, is extremely far removed from simufilam. The tortured theory is explained herein, but it is implausible.

In my eyes, Cassava is up because retail investors are interested in a "lotto ticket". Alzheimer's is a very big indication and pharmaceutical companies are desperate for drugs which work in this disease. This drug doesn't work, and it is not possible that it does. Nevertheless, the dream of making 50- or 100-times one's money is too irresistible for some.

Powerball is the same.

Introduction

Medicine has fascinated me for as long as I can remember. What separates almost all molecules as inert and useless from just a few thousand molecules that are therapeutic? How do we navigate the search space of 8^20 – 10^60 (Virshup, 2013) druglike molecules to arrive at the smaller set of relevant drugs?

One of the reasons studying medicine is fun, at least to me, is its diverse requirements. Sure, you must learn chemistry—why are hydrogen bonds so important for drugs to work (Bissantz, 2010); how does the human gastrointestinal system attempt to metabolize and neutralize our attempts at making medicine, and how do we circumvent them (Veber, 2002) (Varma, 2010); how do we design a drug for exquisite binding potency to its target? And it makes sense that you have to learn biology—what protein target (Kanehisa, 2021), when we design a drug to interfere with its function, will result in a therapeutic effect?; why do certain diseases happen—what clues should we look for to understand pathogenesis better?; what redundancy mechanisms have evolved so that cells circumvent the effects of our medicines?; how do major organs work? You have to learn medicine, or, what physicians study in medical school—what are the nuances that make proteins come together to become a functional and conscious being?; what is the current state of the art in treating any given disease?; what are clinical trials? You must learn about "clinical science" and statistics, the art of testing medicine—how do we design clinical trials for the maximum information?; why are post-hoc multiple comparisons invalid (Streiner, 2015); what does the FDA want to see?; what kind of toxicology experiments do we need to do (European Medicines Agency, 2009)?

This field is vast and takes a lifetime to learn. But the most important skill one must learn is logic. Deductive reasoning is the most powerful weapon in deciding if a potential pharmaceutical will or will not succeed (Pólya, 1957). Reasoning is emotionless: devoid of passion. It is cold and unsparing: whether the patient is a dying young child or an adult with a double chin, the analysis does not change. Emotions cloud our reasoning. If a friend was involved in the development of the drug, if a family member died of the disease this drug purports to treat, if you studied this mechanism of action in graduate school, if you are in the stock of the drugmaker and are at a major profit or loss—all these things can cloud a dispassionate judgment.

Cassava is a biopharmaceutical company I am well acquainted with. Cassava was formerly named Pain Therapeutics. I learned a lot about Pain Therapeutics and met its then CEO, Remi Barbier, when I started my career on Wall Street around 2005. My boss was Remi's roommate in college. I found Remi to be very kind and inspiring. In many ways, he was a role model. He created his own pharmaceutical company, took it public, and it was worth hundreds of millions of dollars. Pain Therapeutics tried, very hard, to make pain drugs. They did not work as planned and the company eventually pivoted to their now sole asset, simufilam.

We are going to dissect simufilam, without agenda or judgment. You will see that if I have any pre-existing bias which could cloud my judgment, it is in **favor** of Cassava. First, I

knew Remi relatively well decades ago and liked him quite a lot. He is a fellow pharma entrepreneur, and I wish him well. One of the players in the Cassava saga has been arrested by the Department of Justice. I know, first-hand, how unfair and difficult that experience can be. He will learn how it is impossible to defend yourself, it is impossible to make the people who you need to convince that they are wrong—that you did nothing wrong. They will not understand you, they do not know your field, and as zealous advocates for their cause, they will fight you with the might of the government. I believe Dr. Wang's indictment is unjust. Even though his actions seem to be very unethical, and probably illegal, scientific fraud is sadly very common. The far bigger crime, in my eyes, are that of the Cassava executives mishandling of the human clinical data, which has remained unindicted.

I don't like that. But a drug is a drug. They're all the same—the molecule can be characterized, it can be manufactured, and it can be determined to work or not work. The truth is all we care about.

The biggest thinking error I've seen in twenty years of investing in, creating and taking over biopharmaceutical stocks is probability based. There is a prevailing and incorrect view of clinical trials. The idea that a clinical trial is to determine "whether or not a drug works" is partially correct, but misleading. For amateurs, this definition conveys the idea that chance is involved. That perhaps this experiment may randomly work out, and the stockholder will become rich. This is wrong.

Clinical trials, done correctly, are deterministic. There is no chance. The outcome is preordained by the laws of physics: the chemistry of the drug, the biology of the patient, the medicine's interference with the disease pathology. The carefully designed statistics allow us to blend away individual differences, the minute randomness that exists. If there is a potent effect: it will be seen.

Just because a process is deterministic does not mean we can always understand it ahead of time. Simulating the physical interactions which lead to the outcome of the throw of a dice is beyond our greatest supercomputer. Too many atoms doing too many things for too much time. But we can apply what we know about the world to experiments to see what likelihood exists. In a few lines of Python, we can accurately simulate the random behavior of a dice without thinking about atoms of physics.

A simple example of how logic works in drug development: a drug that does not cross the lipophilic blood-brain-barrier will not be able to influence a brain disease. Why not? The drug can't get inside the brain, where the disease is happening. Another: a drug that is metabolized quickly into an inert metabolite that has no affinity for the key drug target cannot work. Why not? The drug has transformed too quickly to interfere with the target protein.

We will use what we know about medicine and logic to prove that Cassava's simufilam **cannot** work. This is sobering news. I am no Cassandra, though. For 90% of medicines, I cannot

predict ahead of time whether they will work or not. With respect to the stock market, the 5% of the medicines you know will work are very much valued as if they will work. The market is efficient. The same generally applies to the medicines that do not work. For some reason, Cassava has a $1.3 billion market value, but its sole drug will not work. In fact, the general understanding among professionals who invest in biopharmaceuticals for a living is the same as mine. I haven't been able to find **one** such professional who thinks simufilam 'has a chance'. Nevertheless, the market value of the stock is substantial. At the same time, one could argue that a bona fide Alzheimer's drug could be worth as much as $50 billion. From that lens, the market believes that there is a 2% chance simufilam is a bona fide Alzheimer's drug. I will convince you that probability is zero.

You may take issue. "Martin—you simply cannot know an outcome ahead of time." You are wrong. If I throw a baseball, I know it will not approach the speed of light and exit the atmosphere. I know it will go somewhere between 20mph and 100mph (I wish!). If I do a trial of my pitch versus a major league pitcher, it will be clear within a few samples, who the professional is. There are trials that can be predicted with certainty. Nevertheless, there is uncertainty in the world: *when* will the trial results be revealed? *Will* the trial results be unaltered and representative of the outcome? *Will* the market react rationally?

Preclinical (Non-Human) Research

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A. Introduction and Overview

Preclinical research starts with biology. A company, using researchers inside its own walls, or outside them via contractors, other companies or universities, will decide on a drug pathway to make a drug which interacts with a protein involved in said pathway. Selecting which biochemical functions to intervene with for which disease is *the* key ingredient of successful drug development. One way to think about this is that there are 7,000 human diseases and more than 20,000 proteins/genes. With 140 million choices, this combinatorial problem has limited solutions: only a few thousand drugs have been shown to be medically active. There would be a 1 in 7000 chance of selecting the right target for the right disease at random.

The actual drug discovery and clinical development components of drug development, in my view, is often comparatively easier. After all, we've been making accurate, structure-based medicines for more than 30 years. We have tools like small molecules, antibodies, nucleic acids and other methods to interrogate the usefulness of interrupting or otherwise regulating a protein's function. The real question is: what protein do we want to make a drug for, and which disease do we hypothesize that will benefit?

Without a solid answer to this question, we have nothing. In the history of drug development, very few drugs were made serendipitously (Lu, 2014). In this era of medicine, nearly none have, and it is unlikely many more will. Given the odds, it's simply unreliable and unreasonable to hope a drug works by accident when we can design medicine with exquisite control.

As you read the following pages, I want you to understand that the likelihood a medicine can work without a *precisely defined* mechanism of action is very low. Even with a reasonable hypothesis and good candidate medicine, clinical trials are daunting and often fail. But without a reasonable target and good candidate (we will prove Cassava has neither in simufilam), a medicine is doomed to have good results in clinical trials, which we will show is consistent with Cassava's results thus far.

1. Alzheimer's Disease

Alzheimer's is one of the final frontiers for pharmaceutical companies. With six to seven million patients (Alzheimer's Association, 2023) (Hampel, 2021) in the United States alone, Alzheimer's Disease ("AD") may become the largest pharmaceutical market of all time. With the most severe sequelae possible, a great AD drug could easily command a $100,000 price (around the price of immunooncology regimens). This means that a truly transformative AD drug could be the first medicine ever to break the $100 billion in annual revenue barrier, which no drug has come close to (Comirnaty, the COVID-19 vaccine reached $39 billion in its short-lived existence, Humira peaked at $20 billion).

Alzheimer's: Amyloid-β Introduction, Is it Too Late to Treat Alzheimer's?

Like most brain diseases, we do not understand Alzheimer's as much as we'd like. The central successful idea in Alzheimer's is the amyloid hypothesis (Hardy, 2002) (Selkoe, 2016) (Hampel, 2021). Those not close to this space may have heard that the amyloid hypothesis is wrong or debunked. **This could not be further from the truth.** In fact, in recent years, the amyloid hypothesis has been completely confirmed, and I will convincingly prove this. Nevertheless, amyloid-β is complex, and it is hard to understand the downstream pathogenesis in this enigmatic molecule. How exactly does it give rise to disease? We only have some clues.

We will spend a lot of time talking about amyloid-β, which for now, you can think of as an undesirable molecule which self-aggregates and is heavily involved in Alzheimer's. It takes decades of amyloid-β buildup (and the brain's reaction) for disease to occur (Scheltens, 2020). Why? In addition to the amyloid-β, an entire cascade occurs which gradually results in synapse and neuron loss. But memories don't die so quickly. Our brains store information in a distributed way. The modern, software-based neural networks are roughly equivalent to our biological neural networks. The brain has 100 billion neurons and 100 trillion synapses (Chialvo, 2010). Like a software-based neural network, *small changes* to the neurons and synapses (which theoretically hold something akin to weights and biases), *including total removal of neurons*, should not hurt memory immediately. Only over time, as with software, would 'pruning' this information result in an ability to recall memories or perform functions (LeCun, 1990).

The amyloid-β AD process is neurotoxic and synaptotoxic. Subclinical disease takes place well before overt symptoms. Only upon noticing symptoms can treatment start in the current paradigm. One may be able to slow or arrest the decline of symptoms if intervention is robust, but this goal has been elusive thus far. Even though it *feels* like reversal is out of the realm of possibility, I would counter that so long as neurons and synapse formation is stable, one can at least *re-learn* the lost information. **Keep in mind this very important issue: If it is too late to treat AD because the disease starts so early—is that a major barrier to success for *any* drug being developed in symptomatic AD?** Could this reason be the primary driver of the 98% failure rate of Alzheimer's drugs (Cummings, 2018) (Kim, 2022)?

Because of the difficulties in conducting long-term AD trials, the only patients *left* to enroll in clinical trials are necessarily symptomatic. This means they may have had an asymptomatic disease process occurring for up to twenty years prior to the onset of symptoms. The problem should be immediately apparent. We do not know if Alzheimer's is irreversible once symptoms begin, but many believe it is. If so, a drug must be able to slow the decline of rapid disease progression. But, if the only 'window' to intervene is pre-symptomatic, the current paradigm dooms virtually *any* attempt to treat Alzheimer's from the start of symptoms.

Even if we had the perfect assays for determining when the subclinical process of Alzheimer's has started, running a clinical trial for two decades is impractical, if not impossible due to cost and intellectual property limitations. Cost for clinical trials scales linearly with time and sample size. Patents only last for 17 to 20 years, with a limited, partial credit awarded for clinical trial development time. It would be helpful to allow companies to pursue very early onset (pre-symptomatic) Alzheimer's trials with fully restorative IP exclusivity periods. Right now, long-term trials are not conducted, presumably due to very large cost (including opportunity cost) and the limited return limited intellectual property exclusivity affords.

The only solution we have is to treat pre-symptomatic patients, some of whom may never go on to develop symptoms, which creates an even more difficult statistical hurdle to show an effect. The field must architect strong diagnostic and prognostic markers, to which regulators and physicians must be comfortable that they act as substantive surrogates for symptoms and disease progression. To redefine the disease biologically with amyloid and tau as biomarkers is a reasonable option, but like measuring PSA in prostate cancer, surrogates have their limitations. With an average 6-year survival from symptom onset, using surrogate endpoints are in the "no man's land" of too long to do an OS trial and too short to rely on.

Amyloid-β – Hypothesis & Biology

The central actor in Alzheimer's is **amyloid-β** (Hampel, 2021). **Amyloid-β** is the processed peptide product derived from **APP** (also known as BAPP), or amyloid precursor protein. There are many "species" of amyloid-β. We are typically referring to the 42-amino acid species, AB_{42}, a 4,000 MW peptide. What is APP? Why do we make it? How can this protein cause so much dread? Are we sure that amyloid-β is to blame?

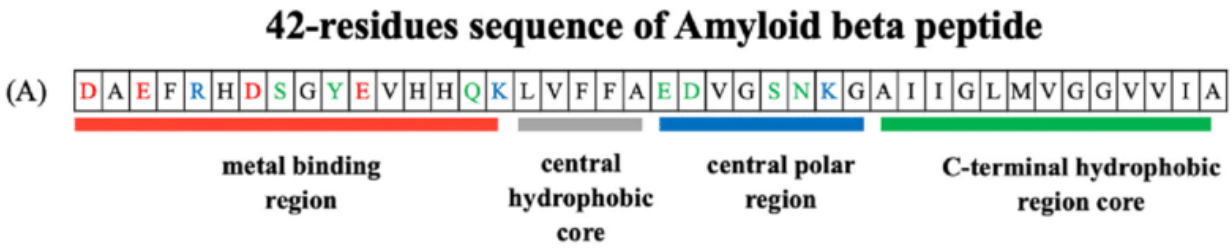


Figure 1: Amino acid sequence of amyloid-β. (Wu, 2021)

APP itself is produced by neurons and other cells. APP is processed by several enzymes, but we will focus on two. β-secretase and gamma-secretase are proteases which "cut" APP to form the various amyloid-β species (usually 40 or 42 amino acids, but there are many). These species vary by length and their ability to self-aggregate. The very name 'amyloid' is a generic term for any substance that self-aggregates. The idea of self-aggregation is that many single amyloid peptides (monomers) will bind to themselves to form two-sized amyloid species (dimers), many-sized amyloid species (oligomers) and even larger metastructures.

These species are deposited **extracellularly**, so keep this in mind as we think about Cassava's therapeutic intervention. Ultimately, amyloid oligomers form stable bodies called 'plaques', which are easily visible in autopsy. It's unclear if plaques are as toxic as oligomers, though data suggests they are not.

Why is the amyloid hypothesis accepted as canon? While there have been some early papers on amyloid and Alzheimer's retracted for errors (and even outright fraud), the amyloid hypothesis has been proven. How? There are three inherited forms of Alzheimer's disease which have mutations in amyloid-β pathways (PSEN1, PSEN2, APP) (Scheltens, 2020) that cause early amyloid deposition. These patients quickly get Alzheimer's at young ages. Another proof of amyloid's involvement in Alzheimer's is Down Syndrome. In Down Syndrome, patients have a third copy of chromosome 21 (trisomy 21). APP is located on chromosome 21! Hence, Down patients have three doses of BAPP when the rest of us have two. Down Syndrome patients accumulate amyloid and have an Alzheimer's like phenotype at an early age.

AD has a significant genetic component that I believe is not well understood (Bellenguez, 2022). Heredity accounts for most of AD risk (Scheltens, 2020)! While the apolipoprotein E (ApoE) alleles are well-known and explain a good portion of AD inheritance, there are other key proteins we will examine. The reason this is critically important is that if we know AD is generally genetic—not only can we design therapies that can intervene in the disease pathway, but we can also exclude mechanisms of action that are unlikely to be beneficial. Keep this in mind, as we will see Cassava's product simufilam is not even close to being related to the genes and proteins implicated in Alzheimer's.

Tau is one of the most important proteins in Alzheimer's. We will have a lot to say about tau later, but the main questions to keep in mind are: does tau come before, at the same time, or after the appearance of amyloid-beta? Does the appearance of tau require amyloid-β? Is amyloid-β required for the spreading of tau's "tangles"?

Amyloid-β accumulates in metabolically active areas which control cognition, such as the prefrontal cortex (Hampel, 2021) (Karran, 2022). But amyloid deposition does not coincide with cognitive deficit—in fact, it precedes it by decades. Also, amyloid-β reaches a plateau in the brain before cognitive impact. This lends credence to the idea that amyloid-β concentration per se is not a continuous driver of Alzheimer's. We can measure amyloid-β with the centiloid scale. Amyloid-positive but tau-negative patients do exist--as many as 25-28% of unimpaired and MCI patients have this classification. On the other hand, tau-positive and amyloid-negative patients are very rare. Only 1-3% of patients have this clinical manifestation. However, if one lessens the tau-positive threshold, as many as 45% of patients without dementia are tau-positive. This disease is sometimes referred to as age-dependent tauopathy and complicates the tau-before-amyloid or amyloid-before-tau question.

Tau plays a very important role in Alzheimer's. Tau neurofibrillary tangles (also known as NFTs) accumulate in cells and cause cellular dysfunction. The interplay between amyloid and tau is unclear, but most believe amyloid pathology drives tau (Karran, 2022). Tau shows up later in the Alzheimer's disease process than amyloid-β. However, tau NFT pathology correlates better with cognitive impairment—possibly because it causes it. Tau can spread in a clinically benign matter before reaching the neocortex. We can measure tau with the PET tracer flortaucipir. There are studies which suggest that a threshold amount of amyloid- β enables tau pathology to spread, and after a certain threshold, further amyloid does not change the rate of tau spread. Tau can be found in young patients before amyloid-β appears. A subtle possibility is that tau appears first, and amyloid-β acts as a driver for tau expansion. All of this considered, amyloid-β is clearly not the only cause of AD pathology.

Inflammation and brain atrophy are common in Alzheimer's. Remember that the brain's immune system differs substantially from the rest of the body. The brain uses microglia to act as the primary immune system. Lewy bodies and TDP43 are also found in AD. Many, including myself, believe that the main damage caused by Alzheimer's is collateral damage via the immune system. Still, we do not completely know how involved microglia are in causing or even suppressing AD.

We do not know why certain *APOE* alleles protect from Alzheimer's and others accelerate it. It is hypothesized APOE binds and clears amyloid-β. There are other genetic clues from the *SORL1, ABCA7 and TREM2* genes (Scheltens, 2020). Most of the polygenic risk scores for Alzheimer's relate to amyloid-β metabolism, immune response, cholesterol and lipid function and metabolism, endocytosis and vascular factors. Probably a smarter strategy for a new Alzheimer's treatment would be focusing on gene therapy to add APOE ε2 protective alleles, or SORL1, ABCA7 expression or TREM2 antibodies (TREM2 is in the clinic). PLCG2 and APP rare mutations also confer protection against Alzheimer's. A CRISPR therapy inducing these changes could be helpful.

The strong success of *APOE* protective alleles raises critical questions. The dramatic protective (or negative) effect suggests that new Alzheimer's pharmaceutical research should focus here for the best results. TREM2 mutants which cause Alzheimer's decrease binding of TREM2 to ApoE, which clears amyloid plaques. Many Alzheimer's risk genes relate to microglial response. To me, it is obvious that the brain struggles to clear amyloid-β, often causing damage in the process, akin to peripheral autoimmune diseases. Note that Cassava's putative mechanism of action, which we will review later, does not have any interaction with ApoE, TREM2 or any of the microglial response.

Although we do not know everything about AD pathophysiology, research has taught us a few things. We do know that metal accumulation does not factor much in Alzheimer's, once a prominent hypothesis. We also know that modulating nicotinic receptors do not seem to change Alzheimer's disease. We know that clearing amyloid-β in and of itself may not be useful. But we do know some amyloid-β clearance mechanisms have worked. Only two Alzheimer's drugs have been FDA approved with clear evidence of effect while 98 have failed pivotal trials. The chances of succeeding at an Alzheimer's drug are ostensibly 2%. This isn't precisely correct for a variety of probabilistic principles, but the odds are certainly not in one's favor.

We've learned that the 5-HT6 pathway, nicotinic alpha-7 pathway, IVIG and other interventions do not work for Alzheimer's. Surprisingly, BACE1/2 inhibitors have not been effective for Alzheimer's despite halting amyloid production, providing a critical clue for mechanisms and pathways to target. There are two amyloid-β monoclonal antibodies which work and are FDA approved: lecanemab (van Dyck et al., 2023) and donanemab.

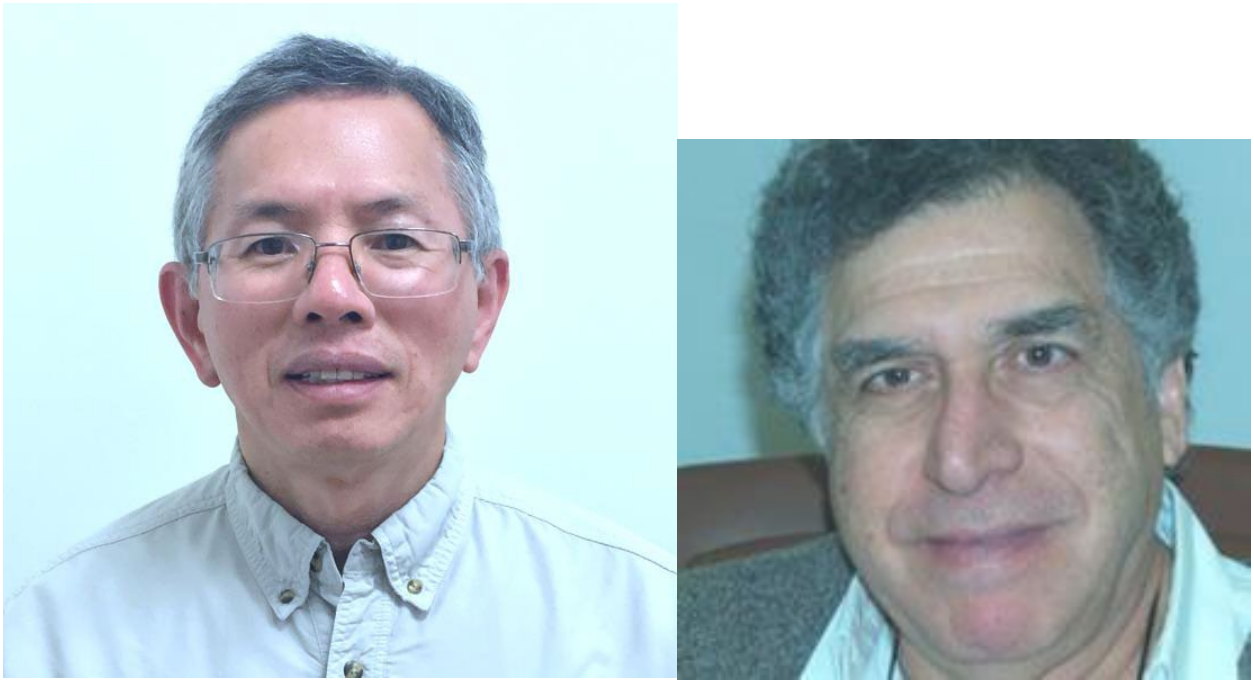
Lecanemab theoretically binds to amyloid-β protofibrils, which is a synonym for oligomers. In theory, these amyloid-β species are more toxic than monomers or insoluble fibrils which are sequestered in plaques. This antibody specificity was not designed for in prior antibody failures. Lecanemab's efficacy is modest, with only a ~2 point benefit in slowing ADAS-Cog increases at 18 months (a roughly 4 point worsening for lecanemab, and 6 points for placebo). Patients with this illness started with ~24 points at baseline. Mild cognitive impairment (or "MCI") is defined as below 11-12 points on ADAS-Cog. On the MMSE test, mild is defined as 21-26 points or 19-23 points more specifically, while moderate is defined as 14-20 points or 10-18 in some cases. No cognitive impairment is defined as 24-30 points. Severe cognitive impairment is less than or equal to 9 points. Lecanemab patients had an MMSE of 25 points, so very mild disease.

Donanemab is similarly effective (Sims, 2023). This antibody targets pyroglutamated amyloid-β.

B. The Curious Dr. Wang

When I get *really* interested in a drug, I start from the beginning. Who invented it? Why? What else were they working on? What was their approach? Dr. Hoau-Yan Wang graduated from China Medical College in 1981. He graduated from Medical College of Pennsylvania, earning a PhD in 1988. Never heard of MCP? It merged with another small medical school and was eventually absorbed by Drexel in 2002. Dr. Wang's PhD advisor was Eitan Friedman, who we'll meet shortly.

Figure 2: Dr. Hoau-yan Wang and Dr. Eitan Friedman



Wang plays a central role in Cassava. His first paper was "Protein kinase C: regulation of serotonin release from rat brain cortical slices", published in Eur J Pharmacol in 1987. His co-author was his supervisor and mentor, Eitan Friedman, also at Medical College of Pennsylvania. Who is Eitan Friedman? He graduated undergrad in 1966 and is Wang's lifelong mentor, collaborator and colleague.

My analysis of Wang's work reveals nothing extraordinary. From 1986 to 1990, he published on serotonin release, PKC, haloperidol, lithium and other topics a neuroscientist biochemist would be researching. This work used the tools of an advanced biochemist: laboratory animals, statistical methods, HPLC, sonication, tissue preparation, radiolabeling and more. Wang did not do chemistry work in any paper.

The early 1990s were a confused era for Wang. He didn't publish much, focusing on serotonin release and other continuations of his earlier work. In 1994, he published a paper on his favorite protein, protein kinase C, and Alzheimer's. He would chase Alzheimer's over the next twenty years.

In 2003, like many big pharmaceutical companies, Wang began researching the nicotinic receptors and their connection to Alzheimer's disease. This line of research has all been abandoned today. This will play a very important role as we seek to understand the simufilam story.

Filamin A

Filamin A is an X-linked protein (Zhou, 2021) which plays a large role in the Cassava saga. Cassava claims that simufilam works by interacting with filamin A. Whenever I look at a drug, I want to know *exactly* what the "binding event" looks like. To work, a putative drug must make some molecular interaction with one or more targets in the patient. The targets should be related to the patient's illness. I like to study this closely. It's fascinating because when drugs form bonds with their targets (usually proteins), they tend to (not always) form a hydrogen bond network. This hydrogen bond network typically disrupts the function of a protein by blocking the ability for another molecule (sometimes a protein) to have its own binding event.

When designing drugs, it is critical to understand the protein target thoroughly. Filamin A is an X-linked intracellular protein whose primary role is to bind actin. Actin is one of the most common proteins in the human body, underlying the cellular cytoskeleton. An interesting way to understand protein function is via deletion in organisms. Humans naturally have mutations in filamin A, and we can induce them in animals. Knocking out filamin or mutating it has adverse impacts. This could make "binding" filamin A, which we will discuss in the chemistry section, dangerous. By interrupting any of the large number of natural functions of filamin A, a filamin A binder may cause toxicity. Alternatively, if it is *not* causing toxicity, we must question if it is a filamin A binder!

Wang claims simufilam binds to the 2561-2565 amino acid region of Filamin A, the "VAKGL" amino acid region. We will talk more about this binding region in the chemistry section, but it is not clear what *if anything* binds to these solvent-facing amino acids. Despite Wang's instance, no literature or database suggests that amyloid-β or the nicotinic receptor binds to filamin A.

The Company's theory is that Alzheimer's patients have an 'altered' form of filamin A. This is not a technical term used in biochemistry. A protein can be mutated, it can have post-translational modifications, it can be misfolded, but 'altered' is not typically used to describes

proteins. Wang and Cassava determined this ‘alteration’ via isoelectric point, which is not intended for this purpose.

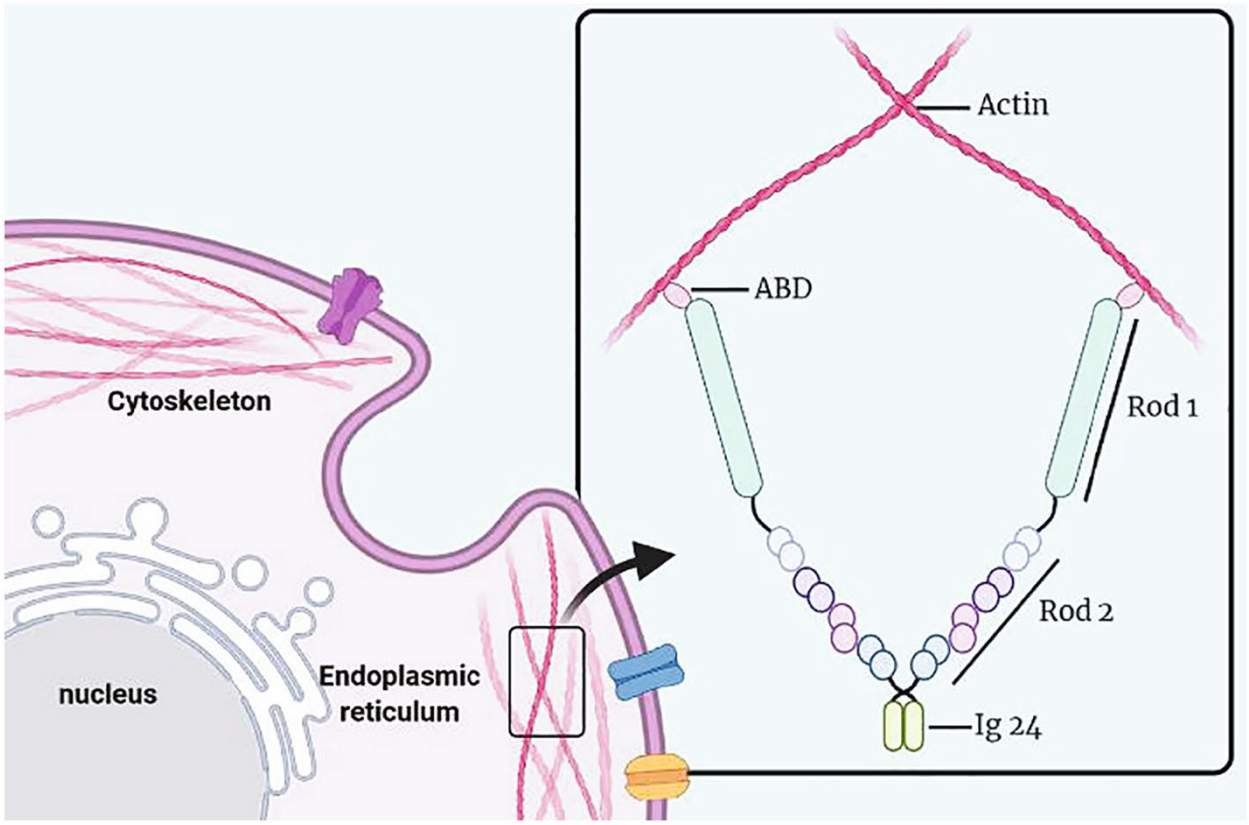


Figure 3: Filamin A schematic.

Nevertheless, the theory Cassava has advanced must be explored. If simufilam binds the VAKGL peptide region of filamin A—which remains to be seen—what is the physiological consequence? The company’s theory is filamin A interacts with three different receptors: nicotinic alpha7, TLR4 and the insulin receptor. The company suggests that by simufilam binding filamin A, the binding of filamin A to the three receptors is terminated. While this is unlikely to be true, we must explore it further. By terminating the “association” between filamin A and nicotinic alpha7, the company claims that the aberrant signaling caused by amyloid-beta at the nicotinic receptor is also abrogated. This syllogism (simufilam binds filamin A effectively enough to have physiological consequences → simufilam binding results in filamin A dissociation from a binding partner → the dissociation induces a distal conformational change sufficient to alter orthosteric binding) is shaky, at best. There is little support for any of the claims, which are outlandish.

One of the reasons to disregard this theory is the extensive work the pharmaceutical industry conducted on the nicotinic space. Unfortunately, pharmacological interventions against

the nicotinic receptor family in Alzheimer's have come up empty (Gault, 2016) (Lenz, 2015) (Frolich, 2011).

Pain Therapeutics/Cassava

Pain Therapeutics was founded in 1998 by Remi Barbier. In 2000, Pain filed its S-1 and went public under the ticker "PTIE", in a deal banked by Robertson Stephens. Pain attempted to develop three different drugs, all of which made it to Phase III and failed.

Remoxy, an abuse-resistant form of oxycodone, was rejected by FDA an astonishing four times. Many abuse-resistant and abuse-deterrent forms of oxycodone have been approved. Some observers of Cassava who also appear to have mental health issues believe that Remoxy's non-approval was caused by Purdue. Purdue filed for bankruptcy in 2019 but had been a target for litigation and substantial regulatory issues for years prior. Despite this, other drugs--including Pfizer's Troxyca (which remarkably includes naltrexone)--were approved (2016).

Pain's ultra-low-dose opioid antagonist failed for IBS. And then, there was Oxytrex. The central idea around Oxytex was that you could combine a powerful opioid, such as morphine, with an opioid blocker such as naltrexone or naloxone, and see *improved* pain relief and *less* withdrawal and side effects than taking the opioid alone. This is very counterintuitive, especially the first part. Opioids generate pain relief by stimulating one of the three opioid receptors: mu (generally the main receptor), kappa or delta. Withdrawing opioids results in the return of pain.

Nevertheless, Pain plowed forward with this flawed idea. In Phase II, a mixed dataset suggested potential success to those ignoring red flags (Chindalore, 2005). In Phase III, they proved that giving an opioid receptor antagonist with an opioid does not paradoxically increase efficacy, but naturally and obviously reduces it (Lynn Webster, 2006).

Table 3. Week 12 Percentage Reduction in Baseline Pain Intensity

	Placebo	*Oxycodone qid*	*Oxytrex qid*	*Oxytrex bid*
Baseline pain intensity	7.7 ± 1.44	7.6 ± 1.36	7.3 ± 1.36	7.6 ± 1.33
Week 1 of fixed dose pain intensity	5.4 ± 2.87	3.9 ± 2.53	4.1 ± 2.51	4.2 ± 2.55
Week 12 pain intensity	5.2 ± 3.05	4.0 ± 2.53	4.2 ± 2.56	4.3 ± 2.55
Week 12 percentage change from baseline	−32.2 ± 38.04	−46.2 ± 33.60*	−41.2 ± 35.15*	−42.6 ± 34.46*

NOTE. Values are mean ± SD.
*$P < .05$ compared to placebo.

While the trials would go on to fail, Pain had already teamed up with Dr. Wang to try and explain why ultra-low dose naltrexone could possibly boost morphine's efficacy. Pain's

employee Dr. Lindsay Burns, who would marry the CEO, Remi Barbier, worked closely with Dr. Wang. They published papers (Tally M. Largent-Milnes, 2008) (Hoau-Yan Wang, 2005) which detail their hypothesis. In brief, the mu opioid GPCR is coupled to G_i and G_o, and activation inhibits the adenylyl cyclase/cAMP pathway. The $G_{\beta\text{-gamma}}$ dimer is released from $G_{i/o}$, which activates GIRK, inhibiting calcium channels and hyperpolarizing the cell.

Dr. Wang had a problem. He needed to explain why Pain Therapeutic's insane ultra-low-dose naltrexone idea was viable. This idea failed when Phase III results of Pain's "Oxytrex", an oxycodone + ultra-low-dose naltrexone drug failed to show any clinical benefit. Pain blamed participant dropouts and bizarrely claimed the drug worked well in patients over the age of 50, an obviously arbitrary and ridiculous subgroup. Wall street didn't believe the subgroup, and evidently neither did Pain, as the drug was scrapped. We believe Cassava Sciences is doing something similar with the "mild" group of their Phase 2 results, which we will discuss later. It is telling that this behavior is repeated by the same CEO, from the same company.

Dr. Wang couldn't really explain the ridiculous ULDN hypothesis. Naloxone and naltrexone work because they inhibit the opioid receptors. Wang contrived this fascinating idea: that naloxone is actually working through binding a protein called filamin A (Wang, 2008). This was highly preposterous given the Oxytrex trial already failed years ago. You should not invent a mechanism of action for a hypothesis which failed. Nevertheless, Wang and Burns persisted in publishing a now retracted PLoS One article making this somewhat astounding claim. We will review this flawed research later.

Timeline of Dr. Wang Research

2000: amyloid-β binds alpha-7 (while at JNJ for <1 year?????)

2005: Oxytrex fails

2008: Oxytrex MOA published by Wang/Burns: filamin A binding changes MOR orientation

2009: Wang published amyloid-β-alpha7 interrupted by GSK drug (this was proven wrong)

2010: patent for simufilam filed as a pain reliever which binds filamin A, again binding changes MOR orientation

2012: Wang publishes small molecule inhibits amyloid-β_{42}/alpha7 formation via filamin.

2015-2016: several alpha7 agonists fail in Alzheimer's

Oxytrex was Pain's second drug. I recall Pain failing to show that the combination of oxycodone and "ultra low dose naltrexone" resulted in any better properties than naltrexone alone. Humorously, the pain relief for Oxytrex was less than oxycodone. This makes sense, because you're giving the antidote with the drug! They also showed a tiny bit of reduction of abuse potential and other undesirable properties. This makes sense because you're giving the antidote! Oxytrex was abandoned.

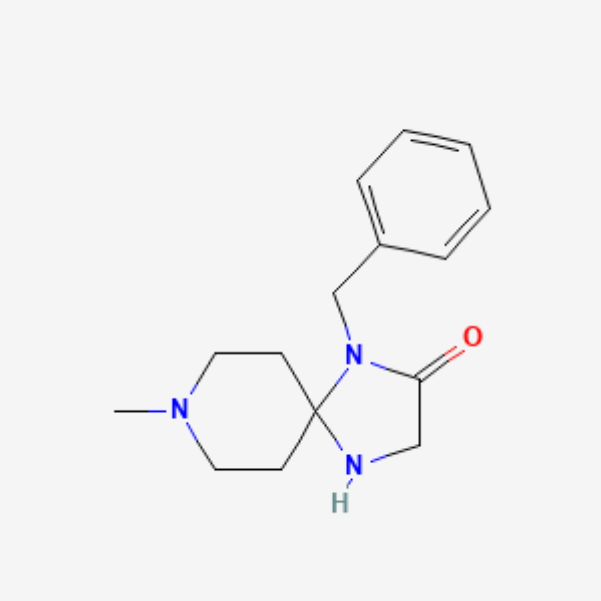
Finally, Pain tried ultra-low-dose naltrexone for IBS. When I called clinical trial sites who enrolled patients in this phase 3 study, they were very excited and believed the trial would work. Despite having probably the most legitimate science of all the Pain Therapeutics candidates, the trial failed.

The idea of ultra-low-dose-naltrexone should give one pause. In pharmaceuticals, very low doses of drugs have very low pharmacodynamics. There are not any drugs I can think of where a very small amount of drug behaves differently from a moderate or a lot of drug. The effect is simply magnified. At a low enough dose, there is no effect at all, at some higher dose the effect begins to appear, and at a higher dose the effect increases, and at some still higher dose, the effect plateaus and does not improve despite even higher doses. This simple idea is called dose response. When you inverted dose response in a drug, you can often assume that drug does not work, since it is not behaving the laws of dose response.

The Drug

Simufilam is a "small molecule". Generally, that means it is a self-contained molecule which will typically not be peptide or protein-based, and therefore amenable to oral administration. Of course, there are small molecules not soluble enough or metabolically resistant to be administered orally. And there are some relatively large molecules that can make it through the GI and "first pass" metabolism.

But, simufilam is rather ordinary from a chemical perspective. It is relatively small at 259 molecular weight. (Recall from high school chemistry: the carbons weigh 12, the nitrogens 14, oxygens 16 and hydrogen weighs 1. Carbons are not indicated with letters, but with lines, and necessary hydrogen atoms are also unlabeled).



The molecular weight of simufilam will become quite important in short order. But, for a small molecule targeting a typical small molecule target (an enzyme, a GPCR/receptor pocket), simufilam is the "right" size. Simufilam also has the "right" hydrogen bond donors/acceptors for Lipinski-like "desirable" pharmaceutical properties. Lipinski is a chemist who theorized most small molecule drugs share these properties. Simufilam, for ordinary targets, would appear safe here. There is only one hydrogen bond donor and three hydrogen bond acceptors. But, when we think about the drug in the context of its binding target, we will see it differently.

How did this drug get discovered? Cassava never published details about this molecule, as is typical in the pharmaceutical industry. My companies, for example, published our discoveries in the illustrious J Med Chem. It's a point of pride for scientists, and Dr. Burns and Dr. Wang did not hesitate to publish preclinical biology data or some human clinical data. But chemistry is notably absent, because **Cassava never had an in-house medicinal chemist.**

Cassava hopes this drug binds to the previously addressed VAGKL peptide sequence in the humongous filamin A protein. But Cassava has never disclosed "crystal-clear" evidence of any binding—typically a crystal structure or co-crystal is done to conduct what chemists call "SAR" or "structure-activity relationship". Without SAR, you cannot design a medicine, because you are "flying blind" as to what you are designing and optimizing.

I examined this region of the filamin A protein and was surprised at what I found.

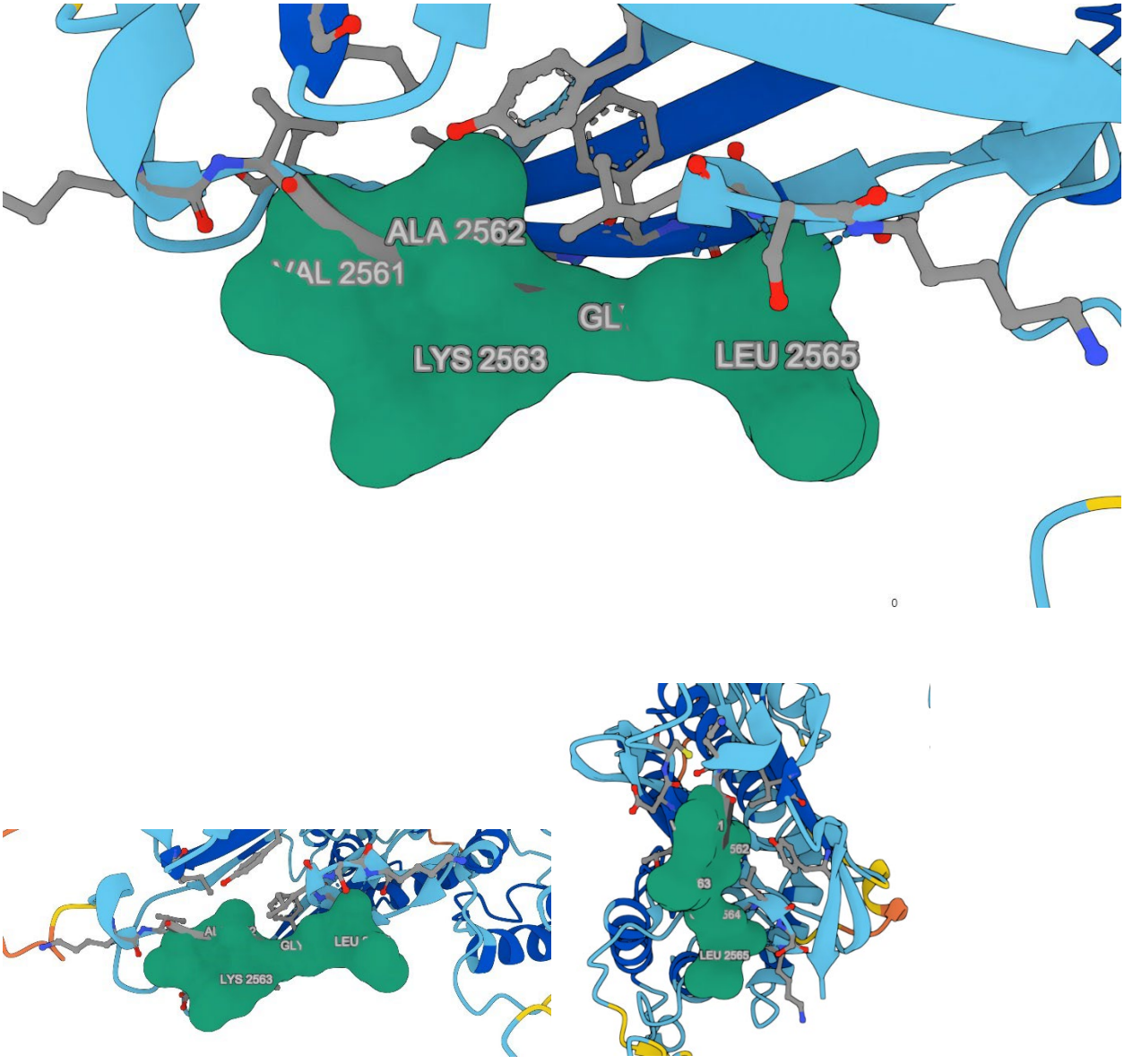


Figure 5: structure of alleged Filamin A binding region

I colored the alleged binding region of simufilam in green. To those untrained in this field, this binding region is almost entirely "solvent-exposed". The solvent in most of these cases is simply water. This is not an "orthosteric" site to my knowledge. Nothing is known to bind specifically at this site, which also makes sense because it would be difficult to form a high-quality bond at this flat surface. Medicinal chemists hate protein surfaces like this because there is very little ability to create "shape complementarity".

Simufilam is a very small molecule. But Cassava purports that simufilam's binding of the green peptide region of filamin A stops *other* proteins from binding to filamin A, presumably at the green region. There is a huge problem here. This kind of drug is called a *protein-protein interaction (PPI) inhibitor*. It is *extremely* challenging to design PPIs. One of the reasons is that PPIs must be rather large to overcome high-affinity binding of proteins to proteins. Why do proteins have such high affinity for each other when they bind? There are an enormous number of places for the proteins to make contact, with each individual hydrogen bond (or other interaction) strengthening the total affinity. Therefore, PPIs must be large and have multiple surface and inner contacts with proteins to work. But, simufilam is tiny and does not have high affinity to this VAGKL region.

This is another bombshell. Cassava claims in various places that simufilam has "femtomolar" potency. This is not something any serious drug developer would ever claim, as even picomolar potency is out of the realm of possibility for most small molecules. Even in Cassava's own patents, simufilam is disclosed as a **micromolar** binder. I still do not believe this data, as it is suspiciously presented.

Figure 5: uM affinity disclosure (compound C0104M). Probably still fake data.

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-continued

FLNA Peptide Binding Assay			
FLNA-binding Compound	Concentration of FLNA-binding Compound		
Compound	0.01 μM	0.1 μM	1 μM
C0044	37.3%	43.9%	50.6%
C0045	39.1%	48.9%	53.7%
C0046	30.8%	35.7%	42.2%
C0050	26.7%	34.5%	36.4%
C0055	29.0%	34.9%	39.5%
C0056	33.7%	38.9%	41.4%
C0060	60.3%	64.0%	68.0%
C0086M	37.9%	48.1%	53.4%
C0087M	51.6%	57.9%	61.5%
C0088M	40.1%	52.4%	56.1%
C0089M	40.7%	46.1%	51.2%
C0090M	42.5%	52.5%	55.8%
C0091M	38.1%	39.8%	46.3%
C0093M	44.8%	49.9%	53.5%
C0094M	43.0%	52.8%	57.5%
C0095M	40.1%	46.6%	50.5%
C0096M	43.0%	48.3%	55.0%
C0099M	46.9%	53.3%	56.0%
C0100M	52.2%	58.2%	64.5%
C0101M	50.5%	56.4%	59.0%
C0102M	52.3%	53.1%	56.6%
C0104M	51.4%	54.1%	55.2%
C0105M	55.7%	62.0%	68.8%
C0106M	45.8%	55.6%	58.9%
C0108M	54.6%	61.4%	68.7%
C0114M	57.1%	63.2%	66.7%
C0115M	47.8%	57.8%	59.9%
C0116M	53.9%	60.0%	62.9%
C0118M	56.6%	61.4%	62.4%

Example 2

FITC-NLX-Based FLNA Screening Assay

A. Streptavidin-Coated 96-Well Plates

Streptavidin-coated 96-well plates (Reacti-Bind™ NeutrAvidin™ High binding capacity coated 96-well plate, Pierce-ENDOGEN) are washed three times with 200 μl of 50 mM Tris HCl, pH 7.4 according to the manufacturer's recommendation.

B. N-biotinylated VAKGL pentapeptide (Bn-VAKGL) (SEQ ID NO: 1)

Bn-VAKGL peptide (0.5 mg/plate) is dissolved in 50 μl DMSO and then added to 4450 μl of 50 mM Tris HCl, pH 7.4, containing 100 mM NaCl and protease inhibitors (binding medium) as well as 500 μl superblock in PBS (Pierce-ENDOGEN) [final concentration for DMSO: 1%].

C. Coupling of Bn-VAKGL Peptides to Streptavidin-Coated Plate

The washed streptavidin-coated plates are contacted with 5 μg/well of Bn-VAKGL (100 μl) for 1 hour (incubated) with constant shaking at 25° C. [50 μl of Bn-VAKGL peptide solution from B+50 μl binding medium, final concentration for DMSO: 0.5%]. At the end of the incubation, the plate is washed three times with 200 μl of ice-cold 50 mM Tris HCl, pH 7.4.

D. Binding of FITC-tagged naloxone [FITC-NLX] to VAKGL.

Bn-VAKGL coated streptavidin plates are incubated with 10 nM fluorescein isothiocyanate-labeled naloxone (FITC-NLX; Invitrogen) in binding medium (50 mM Tris HCl, pH 7.4 containing 100 mM NaCl and protease inhibitors) for 30 minutes at 30° C. with constant shaking. The final assay volume is 100 μl. At the end of incubation, the plate is washed twice with 100 μl of ice-cold 50 mM Tris, pH 7.4. The signal, bound-FITC-NLX is detected using a DTX-880 multi-mode plate reader (Beckman).

Clinical Research

1. Overview
2. NCT03748706 – Phase IIa n=13 Alzheimer's
3. NCT04079803 – Phase IIb n=64 Alzheimer's
4. NCT04388254 – Controlled Withdrawal n=220
5. NCT04994483 – Phase III "RETHINK" n=804 Alzheimer's
6. NCT05026177 – Phase III "REFOCUS" n=1083 Alzheimer's

Clinical Trials

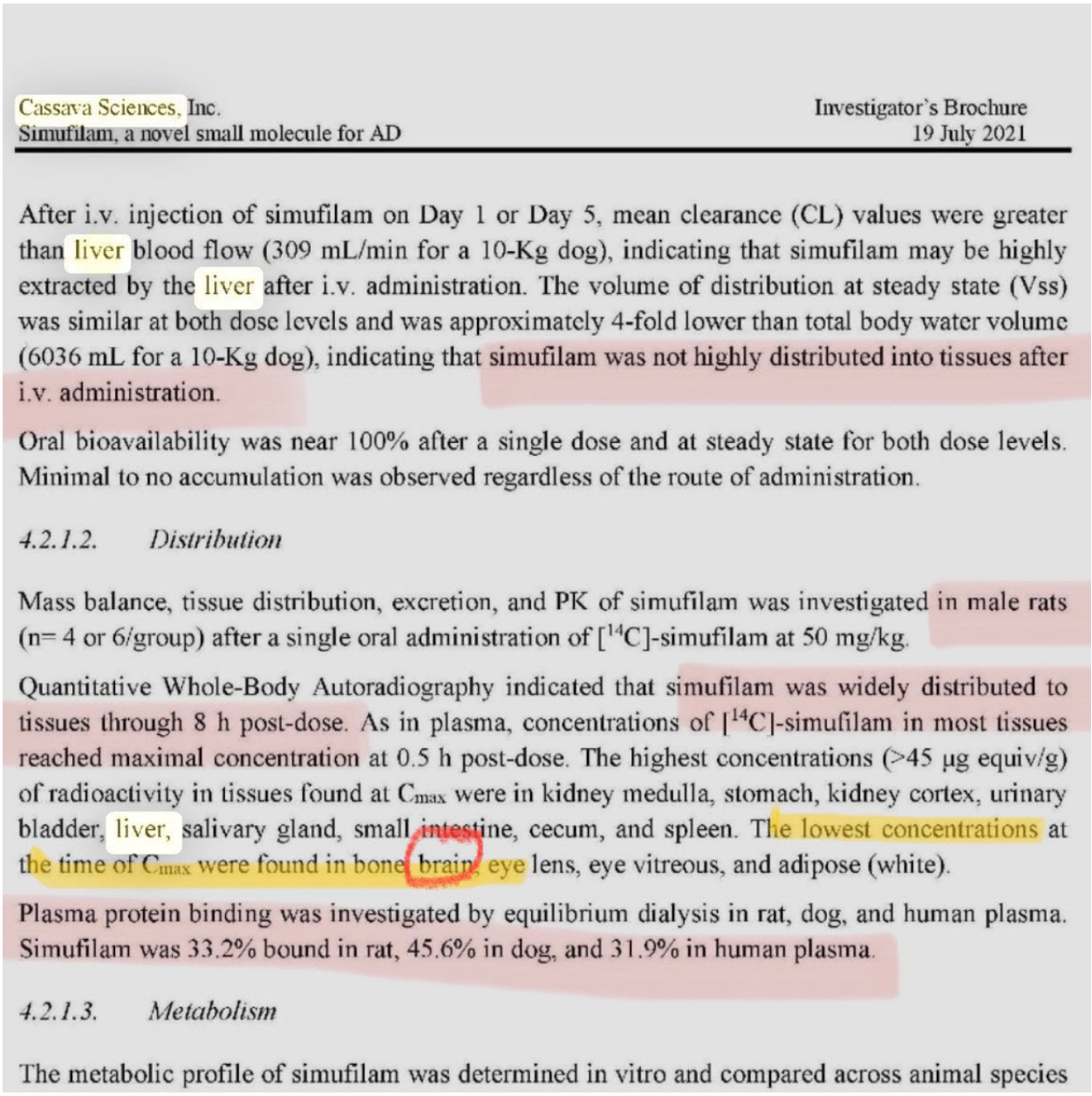
Once a drug has been discovered and tested in animals, assays and any other examination we can throw at it, the time comes for human clinical trials. Cassava started clinical trials of simufilam like anyone else.

Phase I SAD - NCT03784300

The results of this SAD were never published, but the short half-life of simufilam should have given Cassava pause and put priority on a "back-up" compound with better pharmacokinetics. A T1/2 of 4 hours is untenable for a serious pharmaceutical product. But, as is not well known, Cassava should have known better about the poor pharmacokinetics of simufilam. In a non-public investigator's brochure, Cassava disclosed critical details of simufilam problems that it did not disclose to Wall Street. In Figure 4, you can see that Cassava noted that in male rats, simufilam widely distributed to the typical organs: kidney, stomach, liver, etc. But it also disclosed the organs with the lowest concentration: bone and **brain**.

One does not have to be an expert pharmacologist to know that it is not a good thing if your Alzheimer's drug partitions in very low amounts to the brain.

Figure 4: Cassava Investigator's Brochure contains a bombshell about pharmacokinetics.



Cassava Sciences, Inc. Investigator's Brochure
Simufilam, a novel small molecule for AD 19 July 2021

After i.v. injection of simufilam on Day 1 or Day 5, mean clearance (CL) values were greater than liver blood flow (309 mL/min for a 10-Kg dog), indicating that simufilam may be highly extracted by the liver after i.v. administration. The volume of distribution at steady state (Vss) was similar at both dose levels and was approximately 4-fold lower than total body water volume (6036 mL for a 10-Kg dog), indicating that simufilam was not highly distributed into tissues after i.v. administration.

Oral bioavailability was near 100% after a single dose and at steady state for both dose levels. Minimal to no accumulation was observed regardless of the route of administration.

4.2.1.2. Distribution

Mass balance, tissue distribution, excretion, and PK of simufilam was investigated in male rats (n= 4 or 6/group) after a single oral administration of [^{14}C]-simufilam at 50 mg/kg.

Quantitative Whole-Body Autoradiography indicated that simufilam was widely distributed to tissues through 8 h post-dose. As in plasma, concentrations of [^{14}C]-simufilam in most tissues reached maximal concentration at 0.5 h post-dose. The highest concentrations (>45 µg equiv/g) of radioactivity in tissues found at C_{max} were in kidney medulla, stomach, kidney cortex, urinary bladder, liver, salivary gland, small intestine, cecum, and spleen. The lowest concentrations at the time of C_{max} were found in bone, brain, eye lens, eye vitreous, and adipose (white).

Plasma protein binding was investigated by equilibrium dialysis in rat, dog, and human plasma. Simufilam was 33.2% bound in rat, 45.6% in dog, and 31.9% in human plasma.

4.2.1.3. Metabolism

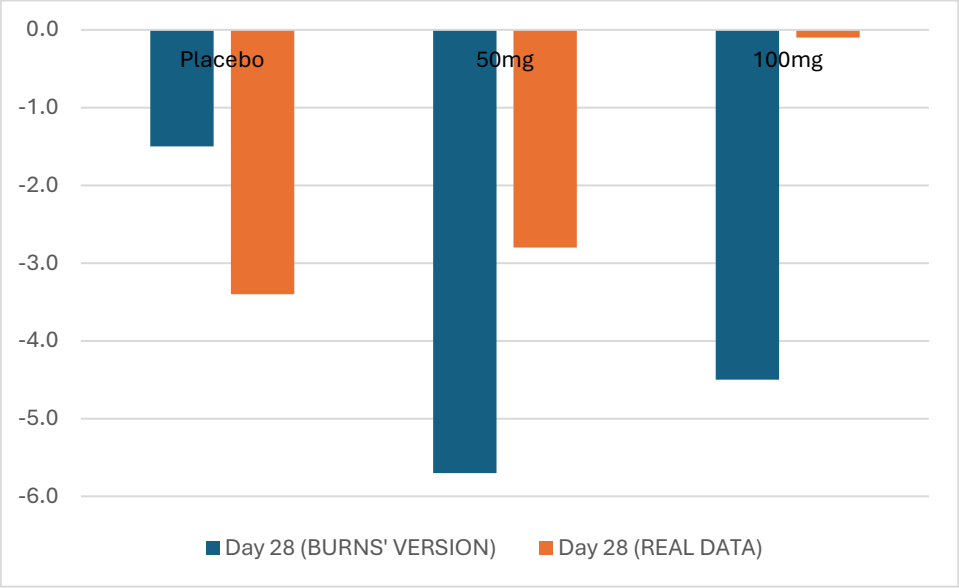
The metabolic profile of simufilam was determined in vitro and compared across animal species

Phase II n=12 NCT03748706

This is the only human clinical study Cassava published, functionally a Phase Ib MAD study. Nothing interesting was disclosed here.

Phase IIA –- NCT04079803 – The Small Failure

This 28-day trial was intended to examine 50mg and 100mg of simufilam against placebo. This trial was designed, as all Phase II trials are, to give hints or directions of efficacy or dose response. As someone who has designed many such trials, this trial comports with the simple fact that this is what Phase II is for. Other Alzheimer's drugs have gone through the exact same process. Phase II is for dose-finding hints and target engagement measurements. The company attempted to do exactly this by studying cognition 28 days after dosing simufilam. The company manipulated the data to appear that simufilam aided cognition, which would be a breakthrough result. Instead, simufilam was *worse* than placebo on cognition.



We learned from the SEC that Burns received the full data set, which showed the orange line. In this test, lower on the chart (more negative number) is better. Burns presumably could not stand the idea of the drug demonstrating the exact opposite of what an Alzheimer's drug could do. Not satisfied in manipulating the data only to show an equivocal outcome, Burns removed nearly half of the data to demonstrate that simufilam aided cognition.

For those who do not follow scientific protocols or experiments, this is a cardinal sin. One practitioner once said it is akin to shooting an arrow and painting the bullseye after the arrow lands. It is extremely unethical, which is why Burns is no longer with Cassava. In my view, this is worse behavior than Wang's! Wang deals in a world of lab science—most of it doesn't replicate. It is inexact, fraught with 'translational' risk. In this trial, Dr. Burns dealt in a

world of humans. It is impossible for Burns to misunderstand just how evil it is to change this data before revealing it. I cannot understate enough how disgusting this is.

Phase IIb Controlled Withdrawal Study– NCT04388254 n=220 (Big Failure)

In the somewhat larger "Phase IIB", Cassava attempted to study simufilam against placebo in a controlled withdrawal study. Again, in Phase II, our goal is to determine hints of efficacy and consider whether the often multi-hundred million dollar investment in Phase III is prudent.

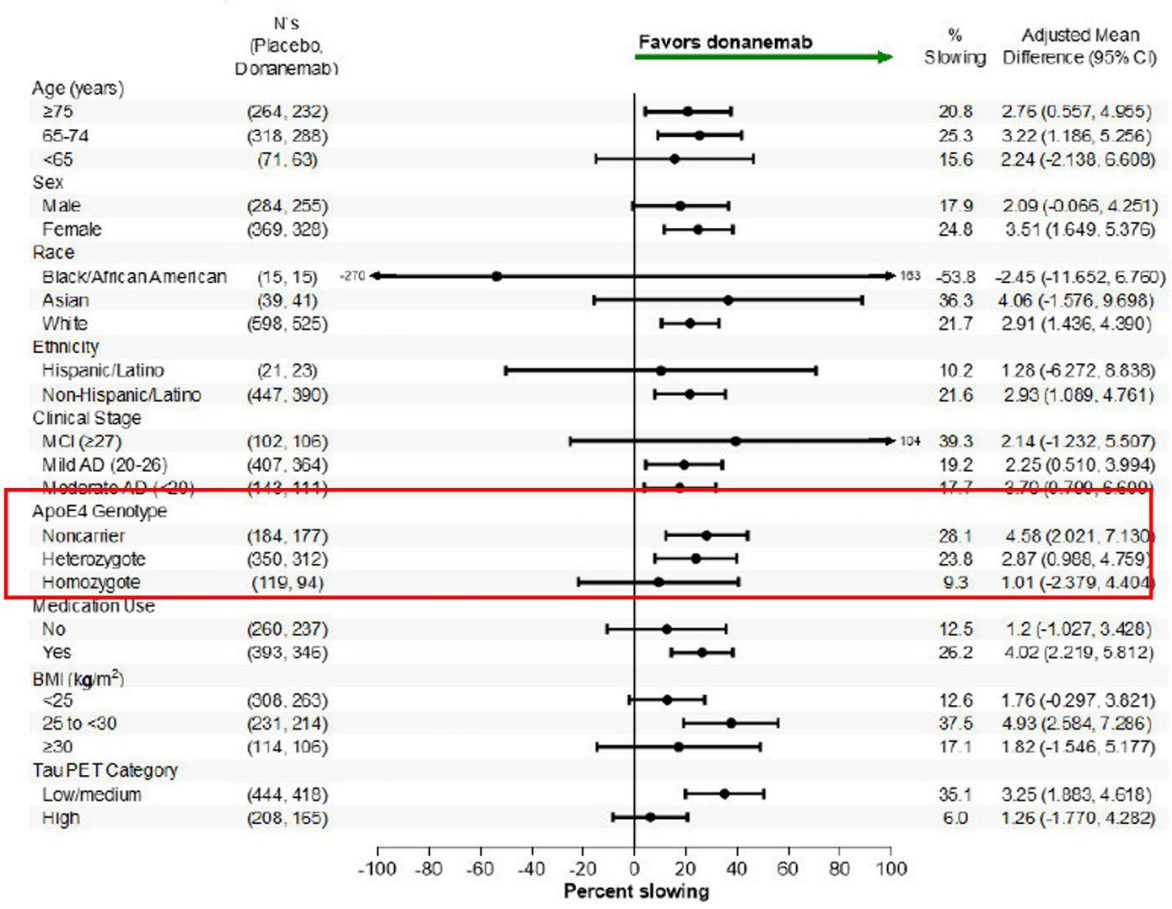
This study began with an open-label period of one year. This is very odd. Normally, one would simply conduct a head-to-head study over 3 or 6 months, or even a year, to determine cognitive changes. Cassava did not do this. After the one year "open-label" period was up, half of the patients remained on drug, and half switched to placebo.

After 6 months, efficacy was measured. Simufilam conclusively failed in a comparison against placebo on the ADAS-Cog scale. It is difficult to trust anything Cassava says about clinical trials after the Phase IIa fiasco. But, assuming their communications are true regarding Phase II, the ADAS-Cog change for simufilam was 0.9 points versus 1.5 points for placebo, a difference favoring simufilam of 0.6 points. Both groups declined by the expected amount during this period. The change between them was meaningless, the company did not provide a p-value in its press release, which would have been very high. Later, they did disclose the p-value at a medical meeting and in other presentations. p=0.45, which would have sent any reasonable pharmaceutical company packing and avoiding spending a single dollar more on this medicine.

The company attempted to deceive investors and itself via a subgroup analysis. A subgroup analysis is conducted by taking a naturally separable filter, such as disease severity, country of trial site, gender, age or any other divider and splitting the data. By splitting the data into two or more subgroups, one naturally creates a subgroup with superior performance. One of the two groups *must* be better than the other. Cassava chose to do this with disease severity. This is a classic post-hoc observation in biopharma that has led to much failure. The narrative typically applies as follows. If the subgroup chosen was milder disease severity, the company simply claims that the sicker patients were 'too far gone' for the drug to work. If the stronger subgroup was more severe, the company simply claims the opposite: the drug only works on patients who are sick enough to benefit from the medicine--it simply can't be given too early before serious disease onset. Of course, the history of medicine proves that neither is true. Drugs like pembrolizumab work very early (adjuvant) and very late (metastatic). Antibiotics work whether you give them prophylactically, immediately, or well after the onset of infection. It is

rare that this dynamic is so pronounced that a simple score can determine whether a drug is completely useless or dramatically useful. There is no such light switch in medicine. It is far more likely that this tool is mostly used to benefit the company in advancing its funding. If the company truly believed that the result was far better in "mild" patients, it would have strictly enforced a "mild" requirement for its Phase III trials. It did not do this. As a final nail in the coffin to the mild vs. moderate thesis, donanemab works regardless of disease severity:

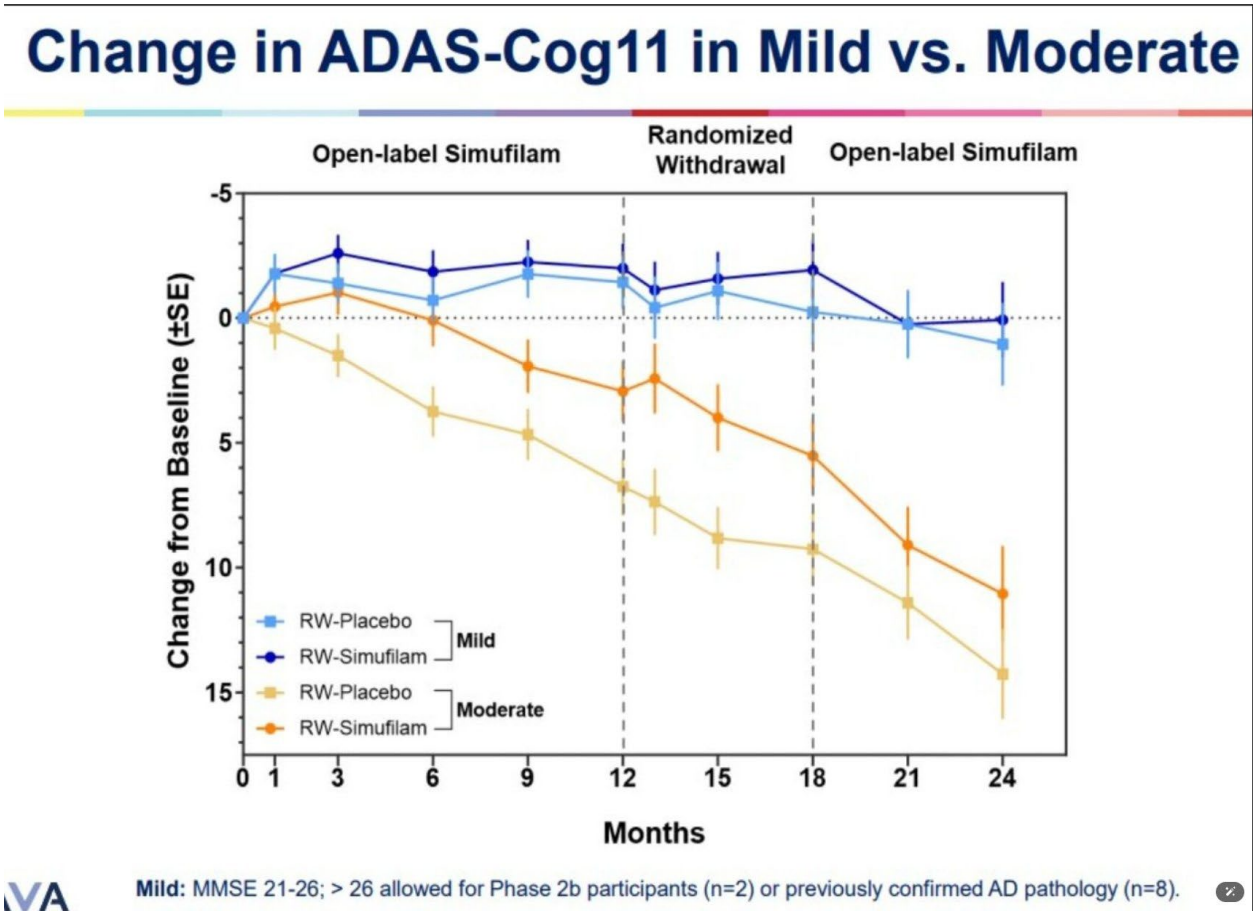
Figure 40: iADRS Subgroup analysis by demographic and baseline characteristics, overall population (AACI-PC period)



Still, some investors believe the open-label results from simufilam during the first year of the trial and the six months following the trial merit consideration. They do not. First, this data has never been published. It's important to publish data so that peers can review it. It sometimes takes an entire year to publish trial results because reviewers will go back-and-forth with authors, questioning their results, poking holes in their statements. If the results are tampered with or there is an attempt to spin the true results, the paper will be rejected from prestigious journals. When the errant paper does get through publication, letters smashing the poorly written papers are often published.

Next, the only controlled period of the trial failed. Open-label trials are necessarily biased. The bull thesis for Cassava is that the stability of cognition seen in the open-label data at 2 years is unprecedented. This is not true. While we can generally disregard open-label data, we must never compare it to rigorous controlled data, which is what some Cassava supporters are doing.

With no paper for Phase IIa or Phase IIb, Cassava suggests that their Phase II "mild" patients did remarkably well. We have several problems with this assertion. The first is that the "mild" cutoff is unclear. What is the average baseline MMSE for these patients? Average baseline ADAS-Cog? How many patients are in this group? We know next to nothing.



We know that the "moderate" patients declined rapidly and the "mild" patients did not decline, even at two years. There are several huge problems here. The first is that open-label data cannot be relied upon for cross-trial comparisons. Without a control group, it is impossible to tell if raters were simply too generous on the subjective ADAS-Cog. It would not be hard to instruct

clinical trial sites of the importance of this Phase II data, and to teach them to err on the side of benefit. A control group removes this potential for bias, which is why it is used.

In one strikingly analogous situation, Cardiff posted open-label results of their cancer drug. The results were astonishingly good, but uncontrolled. The company discontinued the drug despite the unheard of open-label results.

But what if we averaged the mild and moderate groups? This absurd trial resulted in a -0.5 change for mild patients at 24 months and -12.5 change on ADAS-Cog for moderate patients. The total average is therefore -6.5 ADAS-Cog at 24 months. This is roughly the average decline expected in 2 years. In fact, to believe that the mild patients did so well, one must then accept that the drug accelerates cognitive impairment in moderate patients!

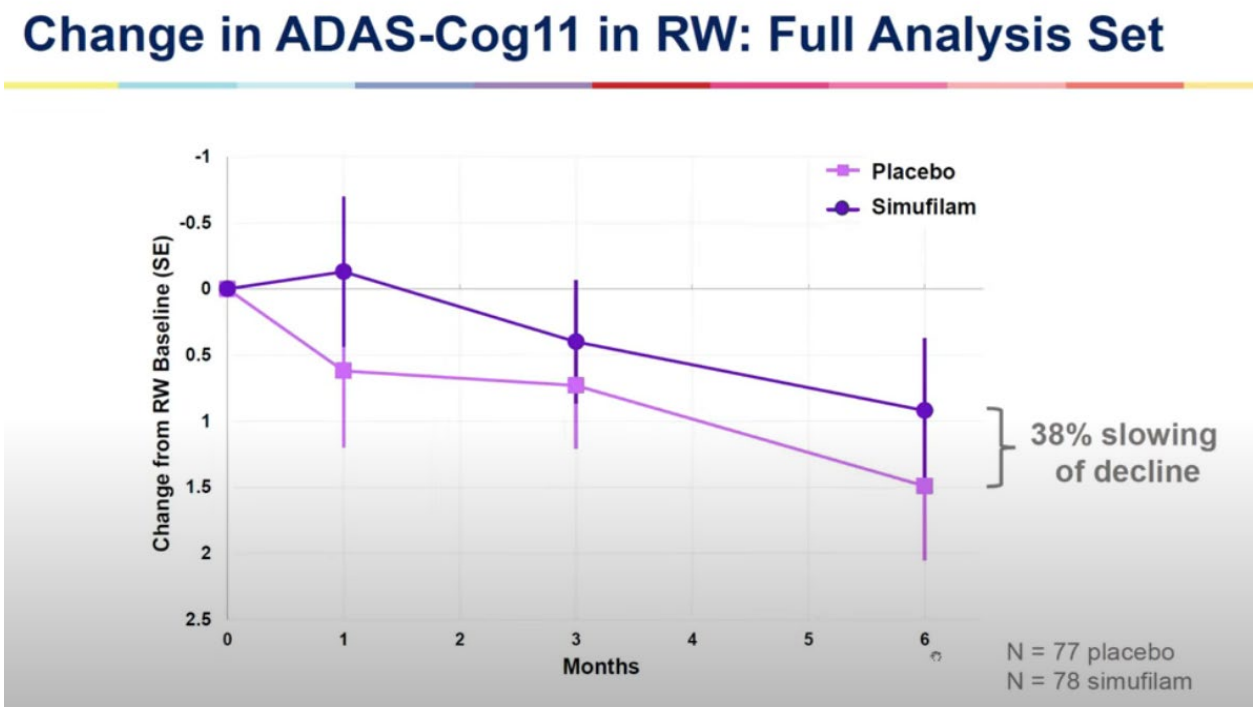
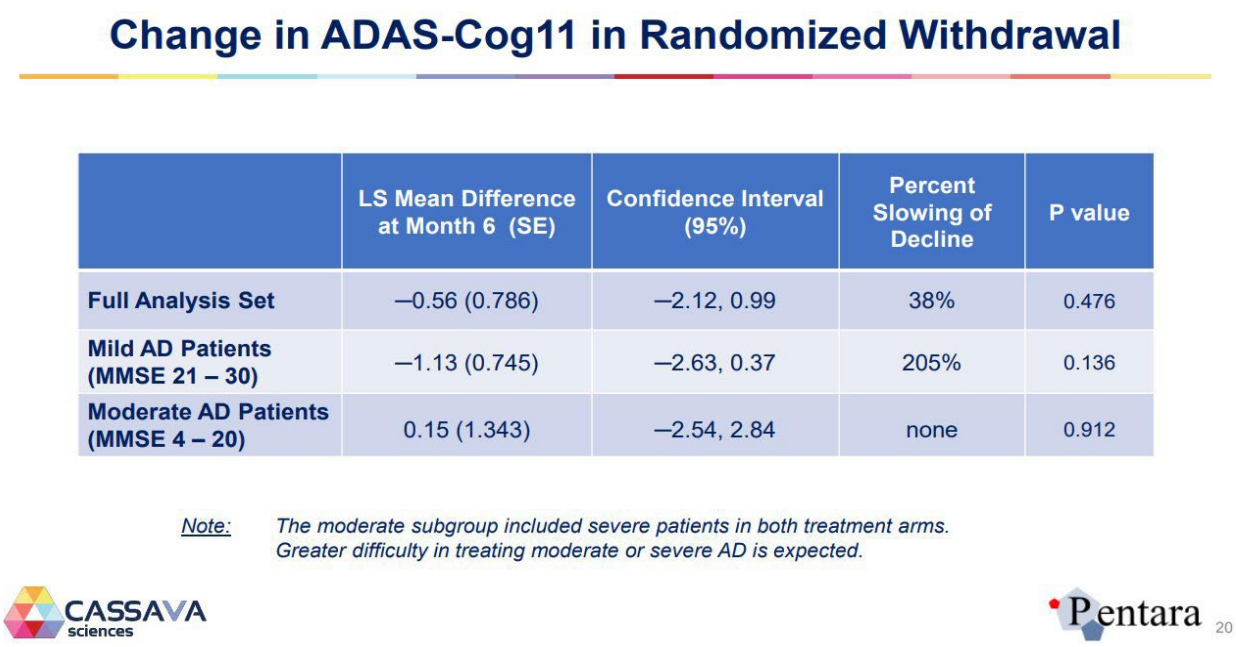


Figure 7: Actual effect of simufilam which Cassava does not like disclosing. Note the lack of a p-value, which was 0.476.

Even if you believe the mild subgroup is a valid observation with a real effect size, that was also not statistically significant! In what might be the worst clinical trial data I've ever seen a company spin, Cassava produces this table:



Change in ADAS-Cog11 in Randomized Withdrawal

	LS Mean Difference at Month 6 (SE)	Confidence Interval (95%)	Percent Slowing of Decline	P value
Full Analysis Set	–0.56 (0.786)	–2.12, 0.99	38%	0.476
Mild AD Patients (MMSE 21 – 30)	–1.13 (0.745)	–2.63, 0.37	205%	0.136
Moderate AD Patients (MMSE 4 – 20)	0.15 (1.343)	–2.54, 2.84	none	0.912

Note: *The moderate subgroup included severe patients in both treatment arms. Greater difficulty in treating moderate or severe AD is expected.*

CASSAVA sciences

Pentara 20

Figure 8: The worst clinical trial data of all-time?

What is misunderstood here is that the mild group not only has a very small post-hoc observation effect size. When you have an *a priori* (ahead of time) primary endpoint, you have a fixed amount of "alpha" to "spend" on analysis. Once you've spent your alpha (typically 0.05) on the primary endpoint, if that endpoint failed, you no longer have any alpha to spend on secondary endpoints or subgroups. This will make sense to you as you read—it is a very common mistake for amateur drug investors to make. Subgroup results are not to be relied upon. In statistics, multiplicity requires an adjustment of p-value. Cassava and their consultants know this. The p-values should be marked "nominal", as they are not valid observations, statistically.

Most new observers refuse to believe this. Why wouldn't it make sense that mild did a little better than moderate? Why can't I rely on this result? The reason is that there are an infinite number of subgroups one could design. We're looking at mild vs. moderate because the other sensical subgroups, generated after the fact, did not have better data—or we would be pushed those subgroups by the company! After finding the best subgroup, the company must retrofit an analysis to explain the findings.

For example, there are results for the controlled withdrawal study regarding ApoE status. Perhaps ApoE e4 patients did better on simufilam than ApoE e3? If they did better than the mild vs. moderate subgroups, the company would simply explain the theory that the drug works best on ApoE e4 patients because it fixes aberrant signaling in that pathway. Or, it could have been the other way around!

One can keep looking for subgroups: male vs. female, time since diagnosis, compliance on protocol, etc. Because of the easy ability to do this, post-hoc data is simply hypothesis generating, at best. The real data is the primary endpoint data, which was as good as a random coin toss. Because there are a large number of reasonable explanations, you can find a subgroup easily. Figure 9 suggests the absurdity of taking multiple comparisons too seriously:

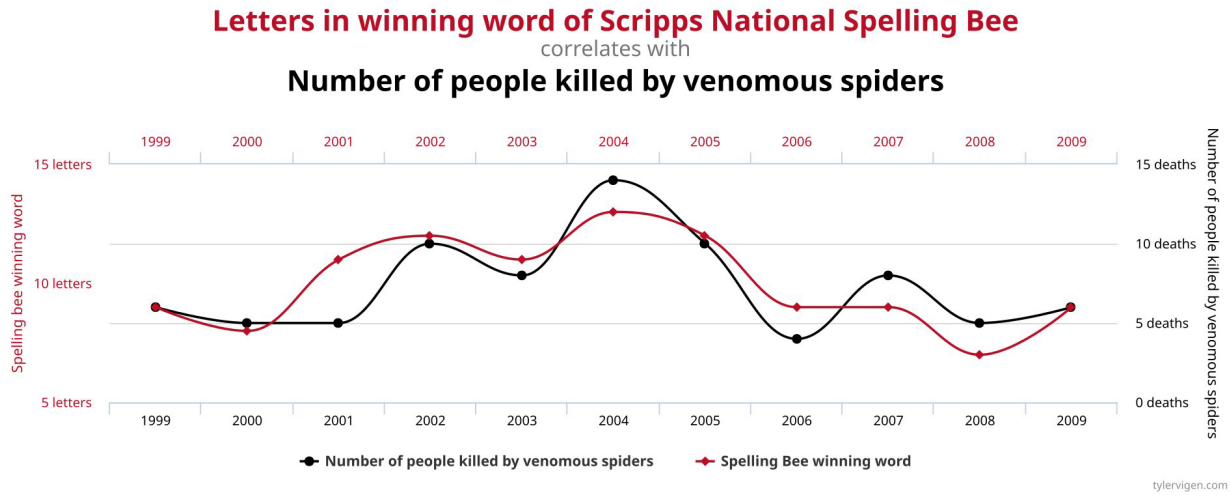


Figure 10: Perils of multiple comparisons.

Decision Making

How do we synthesize our research to make a prediction? One reasonable avenue is the collect the necessary but not sufficient requirements for simufilam to meet the primary endpoint of the "RETHINK" trial. We must be careful to avoid dependent conditions.

Necessary:

- Simufilam binds to filamin with high affinity.
- Simufilam partitions to the brain and has the stoichiometry to modulate filamin A proteins at scale.
- Simufilam is a protein-protein interaction inhibitor, a "refolder" of filamin A, or both.
- Filamin is relevant in Alzheimer's.
- The lack of efficacy in Phase IIa is irrelevant due to a small sample size.

The lack of efficacy in Phase IIb can be explained:

- The failure of the CWS can be overlooked.
- Explanation for the lack of efficacy in Phase IIb is "follow-through" effect from open-label drug.
- Explanation for the lack of efficacy in Phase IIb is mild patients do better than moderate patients.
- Explanation for the lack of efficacy in Phase IIb is that open-label results suggest two-year stabilization of some Alzheimer's patients.
- The "RETHINK" trial is designed well and it is not too late in the disease to intervene.

I suggest that all nine conditions are necessary to overcome the burden of simufilam working in Alzheimer's. I suggest that the probability of all of these being true is very low, which leads to a combined conditional probability of close to zero.

Condition 1: As we've shown, simufilam is unlikely to be a potent binder of filamin. The putative binding region does not correspond well to the simufilam molecule. Data in the simufilam patent is suspicious and not suggestive of a high affinity binder. No crystal structure data, cocrystal, SPR, thermal shift, SAR or other classical chemistry work has been published. The probability that simufilam actually binds to filamin with high affinity and specificity is, at best, 50%.

Condition 2: Simufilam's pharmacokinetic properties are suspect, at best. With a very short half-life and seemingly limited brain partitioning, simufilam is doomed from the start because of these properties.

Condition 3: Simufilam is purported to work as a protein-protein interaction inhibitor. Unfortunately, simufilam's small size precludes it from working as a protein-protein interaction inhibitor, as well as the fact that is very hard to design a protein-protein interaction inhibitor in the first place. Cassava's careless medicinal chemistry campaign did not focus on this.

Condition 4: Filamin must be relevant in Alzheimer's for simufilam to work. We have shown that filamin plays no role in Alzheimer's, a disease which implicates amyloid-β and neuroimmunity. There are no other labs who have publicly replicated Wang's work, which have earned him paper retractions and legal trouble. Wang's work appears to be fraudulent, and his thinking ties together the failed naltrexone hypothesis, conspicuously repurposed to Alzheimer's and tied to his former work in nicotinic receptors. Believing Wang means believing the alpha 7 nicotinic receptor is heavily implicated in Alzheimer's, when alpha 7 drugs have not worked in Alzheimer's. Filamin is one of the weakest links in the simufilam saga, and I believe the likelihood that this is a bona fide target for Alzheimer's is, at best, 10%.

Condition 5: The Phase IIa data doctored by Dr. Burns is shameful to scientific inquiry. Only after seeing the results had been disappointing did Dr. Burns fish for a result that made simufilam look good. These results were met with great support when they were positive. After they turned negative, simufilam supporters suggest there was too little time to see a cognitive benefit. Unfortunately, the numbers are directionally against simufilam, in favor of placebo. The likelihood that we can ignore the failure of the Phase IIa is, at best, 75%.

Condition 6: The Phase IIb controlled withdrawal data was the death knell for simufilam, and no rational pharmaceutical company would have progressed this asset to Phase 3. The *a priori* primary endpoint of the only controlled data for simufilam clearly failed, with a p-value of 0.476 for a -0.56 numerical benefit vs. placebo on ADAS-Cog. This miserable result should suggest Phase 3 is a waste of time, as 'replicating' a -0.56 change vs. placebo is not clinically significant or likely to happen. Even the 'mild' subgroup had a -1.13 change, extremely modest for a fanciful post-hoc observation, and not even nominally statistically significant (p=0.136). Similar to the Phase IIa data, we do not know what data was included, excluded or manipulated from this study, as it was never published.

Believing the Phase II CWS study was positive requires believing three impossible notions.

Condition 7: The first is that the blinded portion of this study showed no difference because patients were washing out of a "disease-modifying" drug that demonstrated a six-month 'lagging' effect. With an extremely short half-life of four hours, it is hard to imagine this being the case. Almost no drugs have this property, other than infectious disease (including tumors) drugs. The possibility that the drug's effect is 'masked' by the remarkable long-lived effect it has is impossible because 'moderate' patients did very poorly while on this medicine. So, the follow-through hypothesis is required to explain why there is so little (zero, in fact) delta between even the favorable subgroup and placebo. The odds we can believe this hypothesis, which is necessary but not sufficient, is 5%.

Condition 8: The very notion of splitting a trial by baseline characteristics to portray success is the calling card of desperate biopharmaceutical companies clinging to hope. History has shown us this is futile. For the trial result of -0.56 ADAS-Cog vs. placebo, there are an infinite number of subgroups which could have been chosen to construct a weighted average-equivalent subgroup thesis. In this case, the arbitrary selection was made between mild and moderate patients, which is theoretically pleasing. The argument is "moderate patients are too far gone to treat". We've proven this is a foolish theory to rely on.

Condition 9: The conceptually "remarkable" 2-year open label data is only convincing if you completely ignore the moderate patients and the fact it was an open-label data set. Comparing this data to placebo-controlled data arms is invalid.

Condition 10: The simplest explanation as to why simufilam won't work is that nothing has worked yet in Alzheimer's. We don't understand the disease well enough to intervene, and it appears we have to intervene early enough. There is a good reason why 98% of Alzheimer's Phase 3s have failed. Simufilam does not overcome any of those problems.

References

Alzheimer's Association. (2023). 2023 Alzheimer’s disease facts and figures. *Alzheimer's Dement*, 1598-1695.

Barbier, L. (2016). *United States Patent No. 9,340,558 B2*.

Bellenguez, C. (2022). New insights into the genetic etiology of Alzheimer’s disease and related dementias. *Nature Genetics*, 412-436.

Bissantz, C. (2010). A Medicinal Chemist’s Guide to Molecular Interactions. *J Med Chem*, 5061-5084.

Chialvo, D. (2010). Emergent complex neural dynamics. *Nat Physics*, 744-750.

Chindalore, V. (2005). Adding Ultralow-Dose Naltrexone to Oxycodone Enhances and Prolongs Analgesia. *J Pain*, 392-399.

Cummings, J. (2018). Lessons Learned from Alzheimer Disease: Clinical Trials with Negative Outcomes. *Clin Transl Sci*, 147-152.

Doody, R. S. (2008). Effect of dimebon on cognition, activities of daily living, behavior, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. *Lancet*.

European Medicines Agency. (2009). ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals .

Frisoni, G. (2021). The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. *Nat Rev Neurosci*, 53-66.

Frolich, L. (2011). Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: a phase IIb dose-finding study. *J Alzheimers Dis*, 363-374.

Gault, L. M. (2016). ABT-126 monotherapy in mild-to-moderate Alzheimer's dementia: randomized double-blind, placebo and active controlled adaptive trial and open-label extension. *Alzheimers Res Ther*, 44.

Hampel, H. (2021). The Amyloid-β Pathway in Alzheimer’s Disease. *Mol Psych*, 5481-5503.

Hardy, J. (2002). The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science*, 353-356.

Hoau-Yan Wang, e. a. (2005). Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor–G protein coupling and Gβγ signaling. *Neuroscience*, 247-261.

Kanehisa, M. (2021). KEGG: Integrated database of genes, pathways, diseases, and drugs. *Nucleic Acids Res*, D545-D551.

Karran, E. &. (2022). The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics. *Nature Rev Drug Discov*, 306-318.

Kim, C. K. (2022). Alzheimer's Disease: Key Insights from Two Decades of Clinical Trial Failures. *J Alz Dis*, 83-100.

LeCun, Y. (1990). Optimal Brain Damage. *Adv Neur Inf Proc Sys*.

Lenz, R. A. (2015). Adaptive, dose-finding phase 2 trial evaluating the safety and efficacy of ABT-089 in mild to moderate Alzheimer disease. *Alzheimer Dis Assoc Disord*, 192-199.

Lu, G. (2014). The Myeloma Drug Lenalidomide Promotes the Cereblon-Dependent Destruction of Ikaros Proteins. *Science*, 305-309.

Lynn Webster, e. a. (2006). Oxytrex Minimizes Physical Dependence While Providing Effective Analgesia. *J Pain*, 937-946.

Mintun, M. A. (2021). Donanemab in Early Alzheimer's Disease. *N Engl J Med*.

Pólya, G. (1957). *How to Solve It.* Princeton University Press.

Scheltens, P. (2020). Seminar: Alzheimer's Disease 2020. *Lancet*.

Selkoe, D. (2016). The amyloid hypothesis of Alzheimer's disease at25 years. *EMBO Mol Med*, 595-608.

Sims, J. (2023). Donanemab in Early Symptomatic Alzheimer Disease The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*, 512-527.

Streiner, D. (2015). Best (but oft-forgotten) practices: the multiple problems of multiplicity—whether and how to correct for many statistical tests. *Am J Clin Nutr*, 721-728.

Tally M. Largent-Milnes, e. a. (2008). Oxycodone Plus Ultra-Low-Dose Naltrexone Attenuates Neuropathic Pain and Associated -Opioid Receptor–Gs Coupling. *J Pain*, 700-713.

van Dyck, C. H. (2023). Lecanemab in Early Alzheimer's Disease. *N Engl J Med*.

Varma, M. (2010). Physicochemical Space for Optimum Oral Bioavailability: Contribution of Human IntestinalAbsorption and First-Pass Elimination. *J Med Chem*, 1098-1108.

Veber, D. (2002). Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J Med Chem*, 2615-2623.

Virshup, A. (2013). Stochastic Voyages into Uncharted Chemical Space Produce aRepresentative Library of All Possible Drug-Like Compounds. *J Am Chem Soc*, 7296-7303.

Wang, H.-Y. (2008). High-affinity naloxone binding to filamin a prevents mu opioid receptor-Gs coupling underlying opioid tolerance and dependence. *PLoS One*, e1554.

Wang, H.-Y. (2022). *United States Patent No. 11,385,221 B2*.

Wang, H.-Y. (2023). *United States Patent No. 11,661,580 B2*.

Wu, K. Y. (2021). Modeling structural interconversion in Alzheimers' amyloid beta peptide with classical and intrinsically disordered protein force fields. *J Biomol Struct Dyn*.

Zamloot, M. (2024). *Untied States Patent No. 12,065,440 B2*.

Zhou, J. (2021). The function and pathogenic mechanism of filamin A. *Gene*.