Disclaimer: The author of this paper is short shares of Anavex Life Sciences (NASDAQ: AVXL)

Anavex Life Sciences: A Decadeslong Drug Doomed for EMA Rejection

(NASDAQ: AVXL)

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First for:

Two Factor
Capital Management

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Executive Summary

- Anavex Life Sciences (NASDSAQ: AVXL) has lodged a marketing authorisation application (MAA) with the European Medical Agency.
- The MAA is for blarcamesine, an orally administered Alzheimer's Disease (AD) drug. The EMA takes up to 210 days to review such applications.
- The EMA recently rejected Eli Lilly's donanemab, a drug with much more comprehensive trials and safety/efficacy data.
- The catalyst for the trade is the EMA rejecting Anavex's MAA; stock will drop 70-80%+ upon rejection.
- AVXL has a financial history mired in controversy, including massive shareholder dilution, class-action lawsuits, and stock pumping schemes.
- There are numerous irregularities within blarcamesine's clinical data, all of which will hinder approval odds.
- The drug failed one of its coprimary endpoints (ADCS-ADL), a measure of patient functionality, and crucial for EMA approval.
- The pharmacological properties of blarcamesine are implausible; the drug shows zero statistical significance until the 48-week mark, despite being a type of muscarinic, which is a fast-acting drug.
- The market assigns a probability of EMA approval at around 30%; I estimate true approval odds to be 2.5-3.5%.
- Overwhelmingly, the EMA will reject blarcamesine's MAA and the stock will drop to near-cash value. I am short AVXL.

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Part 1: Introduction and Overview

Company Pipeline

Anavex Life Sciences Corp. is a clinical stage biopharmaceutical company engaged in the development of drug candidates for central nervous system (CNS) diseases. The lead drug candidate of the Anavex is ANAVEX 2-73 (blarcamesine) which is in Phase III clinical trial (PMID: 39800452) for the treatment of Alzheimer's Disease (AD). Blarcamesine is also in Phase III clinical trial to treat paediatric patients with Rett syndrome; Phase II clinical trial for the treatment of Parkinsons disease; and preclinical trials to treat epilepsy, infantile spasms, Fragile X syndrome, Angelman syndrome, multiple sclerosis, and tuberous sclerosis complex.

Anavex is also advancing ANAVEX 3-71, in Phase I clinical trial for the treatment of frontotemporal dementia and other dementia indications. Anavex also has ANAVEX 1-41, ANAVEX-1066, and ANAVEX-1037 in its clinical pipeline, covering indications including neuropathic and visceral pain, and prostate and pancreatic cancer. Currently, Anavex is awaiting a European Medical Agency (EMA) decision as to whether blarcamesine can be brought to market in the EU, via a Marketing Authorisation Application (MAA). The application is supported by the phase IIb/III ANAVEX 2-73-AD-0004 trial. The drug this report will focus on is blarcamesine for the indication of AD.

Alzheimer's Disease

Dementia is a heterogenous class of disease based on etiological factors, pattern of impairment, course of dementia, and, through laboratory imaging tools, distinct subtypes of dementia are identifiable. Alzheimer's Disease is the most common form of dementia, followed by vascular dementias (VaD) or mixed forms of both (Prabhu, 2022). AD has long been considered an endgame indication for pharmaceutical companies; there are around 6-7 million patients in the United States alone, and 55 million people living with the disease globally (NIH, 2023). Since little foundational knowledge exists about AD, and so many living with the disease, it stands to reason pharmaceutical companies would have a large interest in treating the disease. Currently, there are three FDA-approved drugs available to treat patients with mild-moderate AD, though these are not curative and are unable to stop the disease from worsening over time; all are cholinesterase inhibitors, boosting brain levels of acetylcholine (Galantamine, Rivastigmine, Donepezil). There are two FDA approved drugs for mild AD patients (Lecanemab and Donanemab), which target removal of Aβ (amyloid beta) plaque. There are very few treatment options available considering the huge effect size of the disease, and an academic review of AD drug development found that there have been 98 unique compound failures in 2004-2021. A truly effective AD drug could easily garner billions, if not tens of billions, in annual revenue, since the disease is still largely ineffectively treated by existing medication (Kim C. K., et al., 2022) and no drug exists that can *reverse* cognitive decline, only slow it. If Anavex were to even prove more efficacious compared to existing therapies (the 'mabs') then a potential multibillion dollar revenue stream would be open to the company. This paper will provide reasonable grounds for suspicion of the company, the drug, and ultimately, EMA approval.

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A History of Anavex Life Sciences

Anavex is not a new company; form 10k filings show it was incorporated in 2001 in New York and became a wholly owned subsidiary of 'Thrifty Printing Inc.', who were in the business of 'providing on-line photofinishing services through [Thrifty Printing Inc's] website'. Thrifty Printing is an extremely obscure company – a 10-Q form from 2006 indicates it was incorporated as a Nevada company, but has a registered address in British Colombia, Canada. Specifically, the address is registered to 4837 Canyon Ridge Crescent #101, which is a small single-storey residential address, presumably the home address of Mr. Yang Wu, CEO of Thrifty Printing at the time. Thrifty Printing was operating as a printing business until Mr. Athanosios Skarpelos and Harvey Lalach bought 1,662,520 restricted shares of the company, and with a stake of 48.8% of outstanding shares, Skarpelos became the controlling shareholder. Lalach was appointed Director, President, CEO, Secretary and Treasurer of the Company and Yang Wu resigned as President and CEO on April 25, 2006. Thrifty Printing was generating revenue of <$60,000 per year.

Up until January 2007, operations continued as a photofinishing company, until Thrifty merged with its wholly owned subsidiary, Anavex Life Sciences Corp, and changed its name from "Thrifty Printing Inc." to "Anavex Life Sciences Corp". Common stock began trading OTC under the ticker AVXL in January 2007 also. This is a form of backdoor listing, involving entering the public markets via a shell company (Thrifty Printing). Soon after listing, Anavex began promoting its growth strategy for neurodegenerative diseases, and conducting in vivo animal trials for ANAVEX 1-41 and ANAVEX 2-73. Phase 1 clinical trials for blarcamesine began in 2009 for AD, targeting sigma receptors. Between 2009 and 2010 the company began claiming its 'diversified pipeline' of '30+ novel drug candidates' would 'generate $6 billion annually by 2020' In 2013, suspicious trading and paid promotions triggered a halt by the British Columbia Securities Commission. In 2015, Anavex became scrutinised legally when it was the subject of a class action lawsuit, alleging inflated promises, undisclosed paid promotions, and misleading investors resulting in losses for retail shareholders.

Further, more recent class actions have been brought against Anavex, including 2024 lawsuits by Robbins Geller Rudman & Dowd LLP, Levi & Korsinsky LLP, The Gross Law Firm, and the Shareholders Foundation. Anavex has also had dealings with Lincoln Park Capital (LPC), a financial firm renowned for financing failing penny stocks. Anavex sold $10mm of shares to LPC over a 36-month period, and de-facto diluted the stock; in 2013, there were 37 million AVXL shares outstanding, while in 2015 there were 124 million shares, diluting original investor ownership to less than a third.

Anavex's CEO is currently one Christopher Missling, who prior to becoming CEO in 2013, had no evident prior experience in the biotechnology sector; he was the head of investment banking at Brimberg & Co. before becoming Anavex CEO.

The financial history of Anavex is one mired in controversy, including diluting shareholders and pumping the stock, with the outlandish claim that Anavex would be generating $6bn in annual revenue by 2020. Currently, the company has no marketable product, and will continue to have no marketable product, after the EMA rejects blarcamesine for AD.

Part 2: Alzheimer's, Blarcamesine Trial Analysis and Likely EMA Rejection

Blarcamesine (ANAVEX 2-73)

As established, blarcamesine is an investigational oral drug developed by Anavex. It targets neurodegenerative and neurodevelopmental disorders such as AD, Parkinson's, and Rett syndrome. Blarcamesine has a relatively novel function in the AD drug design space; it functions as an agonist of the sigma-1 receptor (SIGMAR1), a chaperone protein found at the interface of the endoplasmic reticulum and mitochondria (Malar, 2023). By activating this receptor, Blarcamesine modulates the functions of various cellular processes and purports to do the following:

1. Calcium signalling between the endoplasmic reticulum and mitochondria is regulated, which is crucial for cell survival.
2. Blarcamesine assists in the proper folding of proteins, reducing endoplasmic reticulum stress.
3. Blarcamesine improves cellular resilience against oxidative stress and apoptosis, processes implicated in neurodegenerative diseases.

Blarcamesine also exhibits agonistic activity at Muscarinic Acetylcholine M1 Receptors, which are involved in cognitive functions like learning and memory, and the NMDA Receptors, Ionotropic glutamate receptors that help regulate synaptic plasticity and memory function (Malviya, 2008). The drug may also reduce Aβ induced toxicity, inhibit tau hyperphosphorylation, and protect mitochondrial function, all features of AD.

This treatment represents a relatively novel approach in the treatment of AD; no major pharmaceutical companies have advanced therapies targeting the sigma-1 receptor for AD, and institutional research into the receptor is very limited, with drug developers mainly focusing on Aβ or tau proteins. PRX-03140, developed by EPIX Pharmaceuticals, is an orally bioavailable selective partial agonist of the 5-HT4 receptor and a ligand for the sigma-1 and sigma-2 receptors, and advanced to phase II clinical trials for the treatment of AD, though discontinued development after these trials failed, and the company announced bankruptcy.

Amyloid-Beta and Tau Protein Hypothesis

The most successful idea in Alzheimer's research is the amyloid hypothesis (Hardy, 2002) (Selkoe, 2016), and despite claims that this hypothesis has been falsified, this is not the case. The amyloid hypothesis represents the best workable hypothesis of the disease.

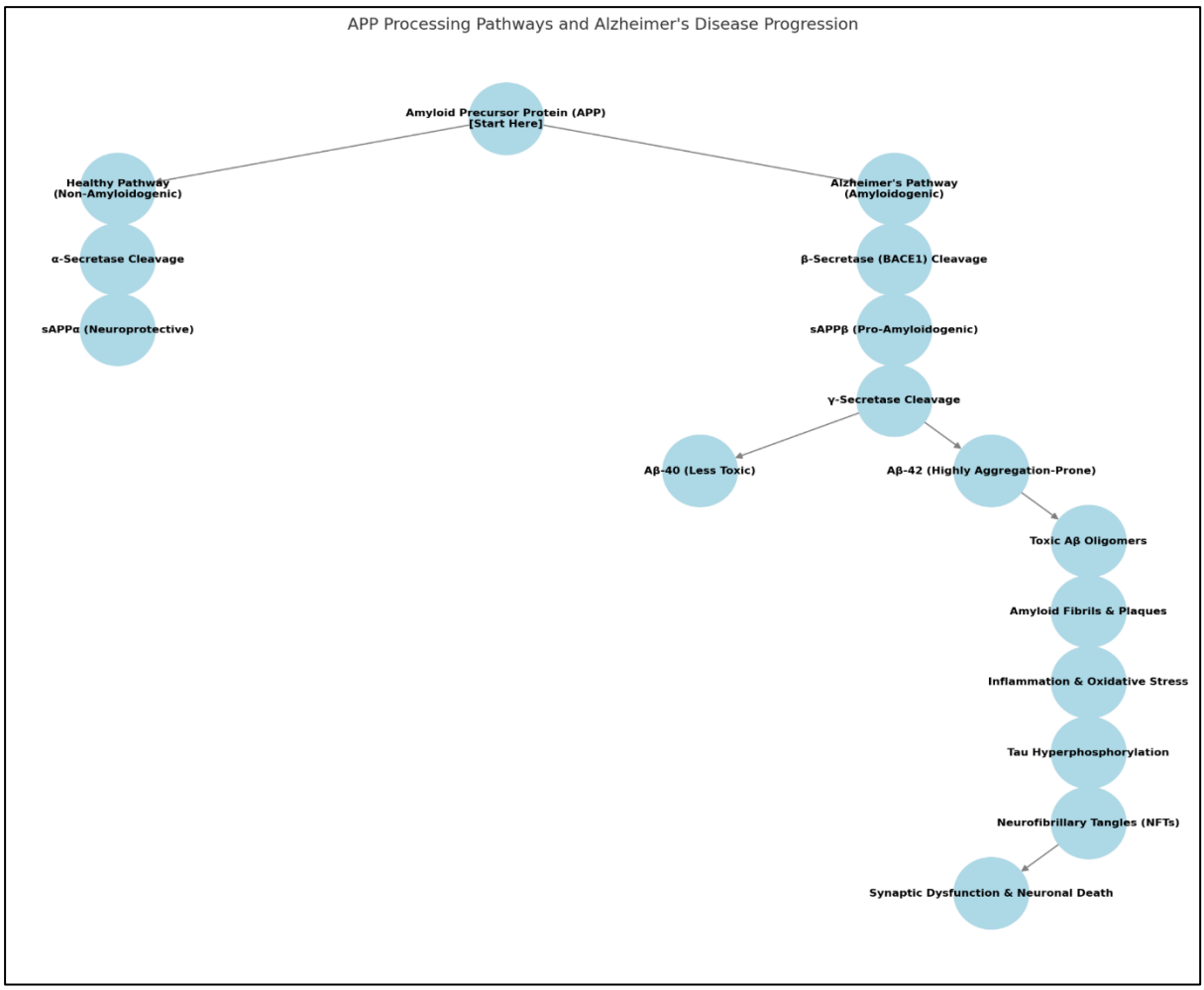
The brain normally produces Aβ to help regulate synaptic transmission, protect from infections, and prevent excessive neuronal activity. Aβ is produced as part of the processing of **amyloid precursor proteins (APP).** APP is a transmembrane protein found in neurons and plays a role in synaptic plasticity, neuroprotection, and repair mechanisms. It is **cleaved by enzymes** into different protein fragments, including Aβ**.** APP can be processed via two pathways: **Non-Amyloidogenic Pathway** (healthy processing); **α-secretase** cleaves APP into **soluble APP-alpha (sAPPα)** which promotes neuroprotection and plasticity, no Aβ is produced. The **Amyloidogenic Pathway** produces Aβ: **BACE1** (β-secretase) cleaves APP first, producing **soluble APP-beta (sAPPβ)**. **γ-secretase** then makes a second cut, releasing Aβ peptides, including **Aβ40** and **Aβ42**. Aβ42 is highly prone to aggregation and is the main component of amyloid plaques (Zhao, 2020).

Enzymes like neprilysin clear excess Aβ and prevent buildup. AD prevents the proper regulation of Aβ/overproduces Aβ, particularly Aβ42, leading to it aggregating into toxic **soluble oligomers**, which interfere with synaptic communication, lead to neuronal hyperexcitability. Oligomers aggregate into **larger fibrils and plaques,** leading to chronic inflammation, oxidative stress, **Tau protein hyperphosphorylation** and **widespread neuronal death** (Cai, 2022).

Tau Protein is a microtubule-associated protein (MAP) inside neurons. It normally stabilises microtubules which act as cellular highways (transporting nutrients, organelles). Tau is **regulated by phosphorylation**, where phosphate groups attach to tau to control its activity. In AD, Aβ triggers Tau to become **hyperphosphorylated** and it loses its ability to bind to microtubules, causing them to break down/degrade and clump together into **neurofibrillary tangles (NFTs)** (Medeiros, 2010).

The **amyloid cascade hypothesis** suggests Aβ **triggers tau pathology** leading to AD progression. AB accumulate first in soluble oligomers, causing inflammation and oxidative stress, making neurons vulnerable (Karran, 2011). Aβ **triggers tau hyperphosphorylation** by activating kinases (enzymes that add phosphate to tau). The **overactive kinases** lead to hyperphosphorylated tau, which detaches from microtubules and starts **aggregating**. The aggregation causes **NFTs** which then spread through the brain; happens in a predictable pattern, moving from entorhinal cortex to hippocampus to cortex. By the time the NFTs are spread extensively, AD

symptoms are severe, suggesting tau is the primary driver of late-stage neurodegeneration, not Aβ.



A Visual Description of APP Processing Pathways and Alzheimer's Disease Progression

The amyloid hypothesis should be accepted as canon despite some early papers being retracted for errors. There are three inherited forms of AD which have mutations in Aβ pathways (PSEN1, PSEN2, APP) (Scheltens, 2020) that cause early amyloid deposition. These patients soon develop Alzheimer's at young ages. Additionally, in Down Syndrome, patients have a third copy of chromosome 21, and APP is located on chromosome 21. Down Syndrome patients have three ‘doses’ of APP while a non-Down person has two; Down patients accumulate amyloid and have an Alzheimer's-like phenotype at an early age.

Although we do not know everything about AD pathophysiology, current research provides clues. Metal accumulation does not heavily influence Alzheimer’s progression. Modulating nicotinic receptors does not change Alzheimer's. Clearing Aβ may not be useful on its own, as seen by Merck’s failed Verubecestat BACE1 inhibitor drug – the drug inhibited Aβ production by 75% yet still showed no clinical effect. Roche and Genentech’s

Gantenerumab also led to lower Aβ plaque burden, but did not show clinical efficacy. J&J, Pfizer, Elan & Wyeth's Bapineuzumab also confirmed this.

This summarises current, foundational scientific understanding of Alzheimer's, and explains why Alzheimer's is so hard to treat; the disease starts so early, making it extremely difficult for *any* drug to effectively mitigate symptomatic AD, and this could be the reason 98% of Alzheimer's drugs end up failing (Cummings, 2018) (Kim, 2022). It is further important to note that Anavex's mechanism of action (MOA) does not interact with microglial responses in AD, has no direct effect on tau proteins or neurofibrillary tangles, and does not directly target Aβ plaques.

Blarcamesine is Muscarinic

Blarcamesine is an orally, once daily administered small molecule for the treatment of Alzheimer's. Blarcamesine acts, primarily, as an agonist of the sigma-1 receptor, and is also an agonist of the muscarinic acetylcholine M_1 receptor, and the ionotropic glutamate NDMA receptor. The drug was first tested in mice against the effect of muscarinic receptor antagonist scopolamine, which induces learning impairment. M_1 receptor agonists (blarcamesine) are known to reverse amnesia caused by scopolamine (Malviya et al., 2008). Muscarinic receptors are also involved in forming short- and long-term memories, and experiments in mice found that M_1 and M_3 receptor agonists inhibit the formation of Aβ plaques (Villard et al., 2010). Stimulation of the M_1 receptor activates AF267B and blocks β-secretase, which cleaves APP, producing the Aβ peptide as established previously. The M_1 receptor hence appears to decrease tau hyperphosphorylation and Aβ accumulation (Leal et al., 2016). More on muscarinic drugs later.

Blarcamesine inhibits mitochondrial respiratory dysfunction and prevents against oxidative stress and apoptosis, while also exhibiting anti-apoptotic and antioxidant activity. These effects are observed because the sigma-1 receptor agonists stimulate the anti-apoptotic factor Bcl-2 due to reactive oxygen species dependent transcriptional activation of nuclear factor kB (Lahmy et. al, 2015).

Existing Treatment and the EMA

There are currently two Aβ monoclonal antibodies (mabs) that work and are FDA approved (aducanumab was discontinued in 2024), Lecanemab and Donanemab. The former works by binding to Aβ protofibrils (oligomers). These oligomers are, as established, more toxic than monomers. The efficacy of Lecanemab is also modest, with a 2-point benefit in slowing ADAS-Cog increases at 18 months. Lecanemab patients had an MMSE score of 25 points.

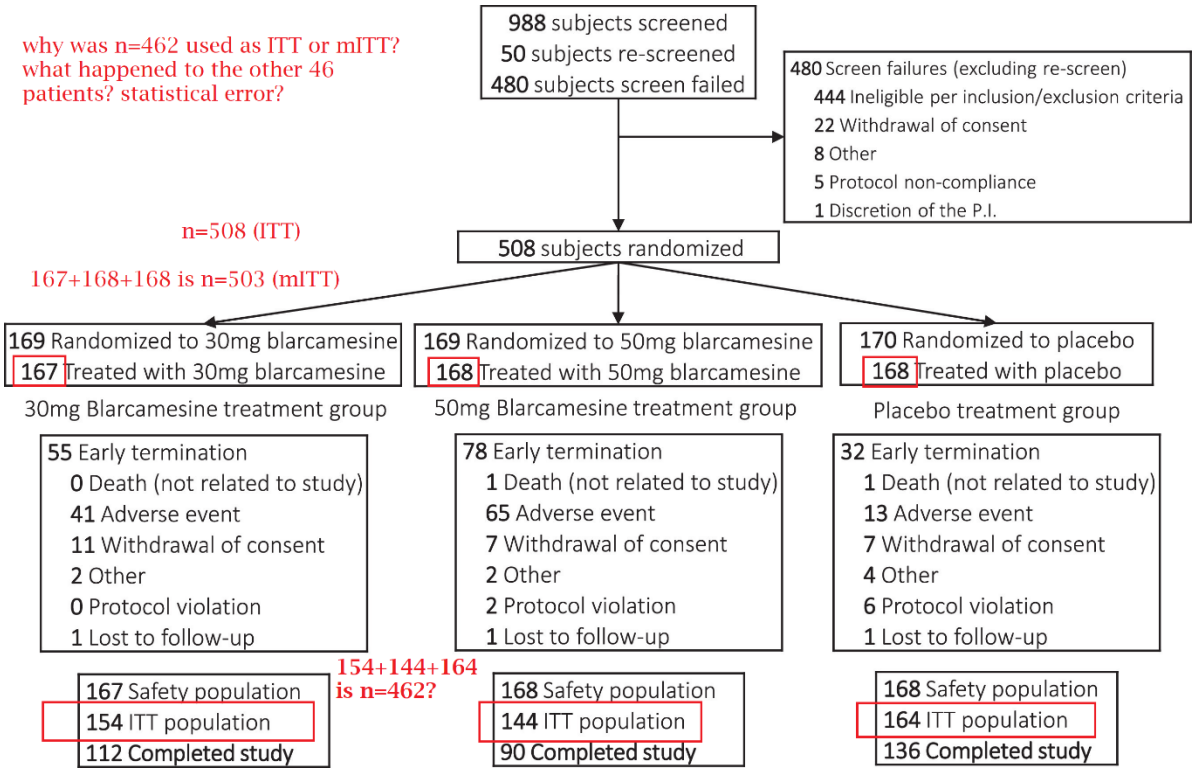
Donanemab has a similar efficacy profile, targeting pyroglutamated Aβ. Crucially, despite FDA approval, **donanemab has been rejected by the EMA.**

This is pivotal for AD drug marketability, and by extension, Anavex's blarcamesine, which has **only been filed for approval in the EU** (they didn't bother filing with the FDA). The Committee for Medicinal Products for Human Use (CHMP), the equivalent of an FDA advisory committee, and the same committee that will be reviewing blarcamesine, rejected donanemab for clinical use, citing high rates of amyloid-relating imaging abnormalities (ARIA incidents), which can result in inflammation or brain bleeding related to the course of treatment. Aducanumab also faced EMA rejection despite amyloid clearance and partial efficacy, Verubecestat also failed despite 75% Aβ reduction.

The EMA, generally, is stricter than the FDA when it comes to Alzheimer's approvals, and blarcamesine will face strict scrutiny under EMA standards. Blarcamesine's Phase IIb/III trials showed statistical significance on the ADAS-Cog13 score, a 2-point advantage vs placebo, which is roughly a 35% slowing of cognitive decline. Blarcamesine failed to improve on the ADCS-ADL functional score, and did not show any significance difference between drug and placebo in activities and daily living (p=0.357). Patients on the blarcamesine arm did not preserve their daily functioning better than the placebo arm over 48 weeks. EMA guidelines for mild AD stipulate that a drug's cognitive benefit must be confirmed by a positive effect on function or a global clinical outcome. The EMA, historically, has been unwilling to accept cognitive change alone as sufficient, and the agency could conclude cognitive change did not translate into any tangible functional improvement. Anavex had noted ADAS-Cog13 and ADCS-ADL as coprimary endpoints; typically, both coprimary endpoints need to show statistical significance in order for a trial to be deemed a success, though Anavex deemed blarcamesine's phase IIb/III trial successful despite a failure of one of its coprimary endpoints. Blarcamesine's approval is also reliant on a single phase IIb/III trial, with the EMA preferring replication of efficacy in at least two such trials for a novel therapy. Donanemab's Phase 3 also showed more robust results (35% slowing on iADRS p<0.001) with consistent benefits on secondary endpoints including CDR-SB (37% slowing) and ADAS-Cog13 (32% slowing), blarcamesine's data is much less uniformly positive with no ADL or iADL benefit. The dropout rate in Anavex's study is also significant, with 35% of patients dropping out of the blarcamesine arm, 32.2% due to treatment emergent adverse events (TEAEs), nearly 1 in 3 patients dropped out of the blarcamesine arm. Blarcamesine was associated with higher rates of dizziness, 35.8% vs 6% in placebo, confused states, 14.3% vs 0.6% placebo, and balance disorder 7.5% vs 0.6% placebo. States like these can cause falls and injuries in elderly patients, and though this wasn't observed in clinical trials, real-world scenarios lack the same level of patient monitoring, hence these states pose a significant risk to patients. There is also methodological weakness in the Anavex trial, which the EMA will likely scrutinise.

Clinical Trial Analysis

Anavex itself was responsible for data collection, analysis, and interpretation, with no independent oversight. There is statistical inconsistency in reporting intent to treat (ITT) and modified ITT (mITT) populations in the blarcamesine IIb/III trial; the ITT population should include **all** patients who were randomised, regardless of if they received the study drug or not. In the study, 508 patients were randomised, so ITT should be n=508. The mITT population includes only randomised patients who received at least one dose of the study drug, there were 503 patients dosed, so *n* should be 503. The Anavex authors claim their primary analysis was based on the ITT population, though report ITT as n=462, which is neither ITT (508) or mITT (503), which means 46 patients were excluded from the study. The authors also equate ITT to mITT which is not standard in clinical trials.



The clinical trial reported in the publication NCT03790709 also has an inclusion criterion of MMSE>=20, yet in an earlier presentation of this same trial, the corresponding author reported that 30 participants had an MMSE score <20. The current report implies that some patients (out of the 68<=20) had an MMSE score <20.

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Eligibility Criteria

Description

Inclusion Criteria:

- Patients aged 60 to 85 years, inclusive, with a NIA-AA diagnosis of mild cognitive impairment (MCI) due to AD or early stage mild dementia due to AD. AD diagnosis should be made by an appropriately qualified medical specialist and AD pathology should be confirmed by either:
  1. Historical records of amyloid CSF assessment or
  2. Historical records of amyloid PET scan or
  3. If neither historical records are available, then AD pathological diagnosis confirmation should be offered at screening:

  i. CSF collection or ii. Amyloid PET iii. Past medical records of MRI or CT are optional.
- Mini Mental State Examination (MMSE) score between 20-28, inclusive.
- Free Recall score ≤17 or Total Recall score <40 on the Free and Cued Selective Reminding Test (FCSRT).
- Participants are either outpatients, or residents of an assisted-living facility. Participant has a designated study partner, who spends at least 10hrs per week with the participant, in order that assessments e.g. carer burden instruments are completed with true knowledge of the participant.

Ages Eligible for Study

60 Years to 85 Years (Adult, Older Adult)

Sexes Eligible for Study

All

Accepts Healthy Volunteers

No

Baseline Clinical Characteristics

Characteristic	Blarcamesine 30 mg (n=154)	Blarcamesine 50 mg (n=144)	Blarcamesine Pooled (n=298)	Placebo (n=164)
Baseline Clinical Scores, Mean (SD)				
ADAS-Cog13	28.4 (8.4)	28.9 (9.1)	28.5 (8.5)	30.4 (8.4)
ADCS-ADL	66.7 (7.4)	67 (7.9)	66.9 (7.6)	66.4 (7.1)
CDR-SB	3.8 (1.6)	3.8 (1.8)	3.8 (1.7)	4.1 (1.8)
MMSE	23.6 (3.1)	23.6 (2.8)	23.6 (2.9)	23.0 (2.7)
Baseline CDR-Global scores, n (%)				
0	0 (0)	1 (0.7)	1 (0.3)	0 (0)
0.5	98 (63.6)	96 (66.7)	194 (65.1)	94 (57.3)
1.0	54 (35.1)	45 (31.3)	99 (33.2)	68 (41.5)
2.0	1 (0.6)	2 (1.4)	3 (1.0)	2 (1.2)
3.0	1 (0.6)	0 (0)	1 (0.3)	0 (0)
MMSE score at baseline, n (%)				
<20	11 (7.1)	9 (6.3)	20 (6.7)	10 (6.1)
≥20	143 (92.9)	135 (93.8)	278 (93.3)	154 (93.9)
Concomitant AD medication, n (%)				
Cholinesterase inhibitors (ChEIs)	102 (66.2)	104 (72.2)	206 (69.1)	108 (65.9)
Memantine	19 (12.3)	17 (11.8)	36 (12.1)	18 (11.0)
Baseline Plasma p-tau (181)				
No. of participants evaluated at baseline	145	132	277	153
Baseline mean (SD), pg/mL	61.88 (25.44)	62.62 (25.75)	62.23 (25.54)	65.42 (28.04)
Baseline Plasma p-tau (231)				
No. of participants evaluated at baseline	102	97	199	123
Baseline mean (SD), pg/mL	29.02 (29.55)	34.19 (50.76)	31.54 (41.24)	27.08 (34.58)

anavex LIFE SCIENCES Corp. 15

Table 1
Demographic characteristics of the Intent-to-Treat (ITT) population.

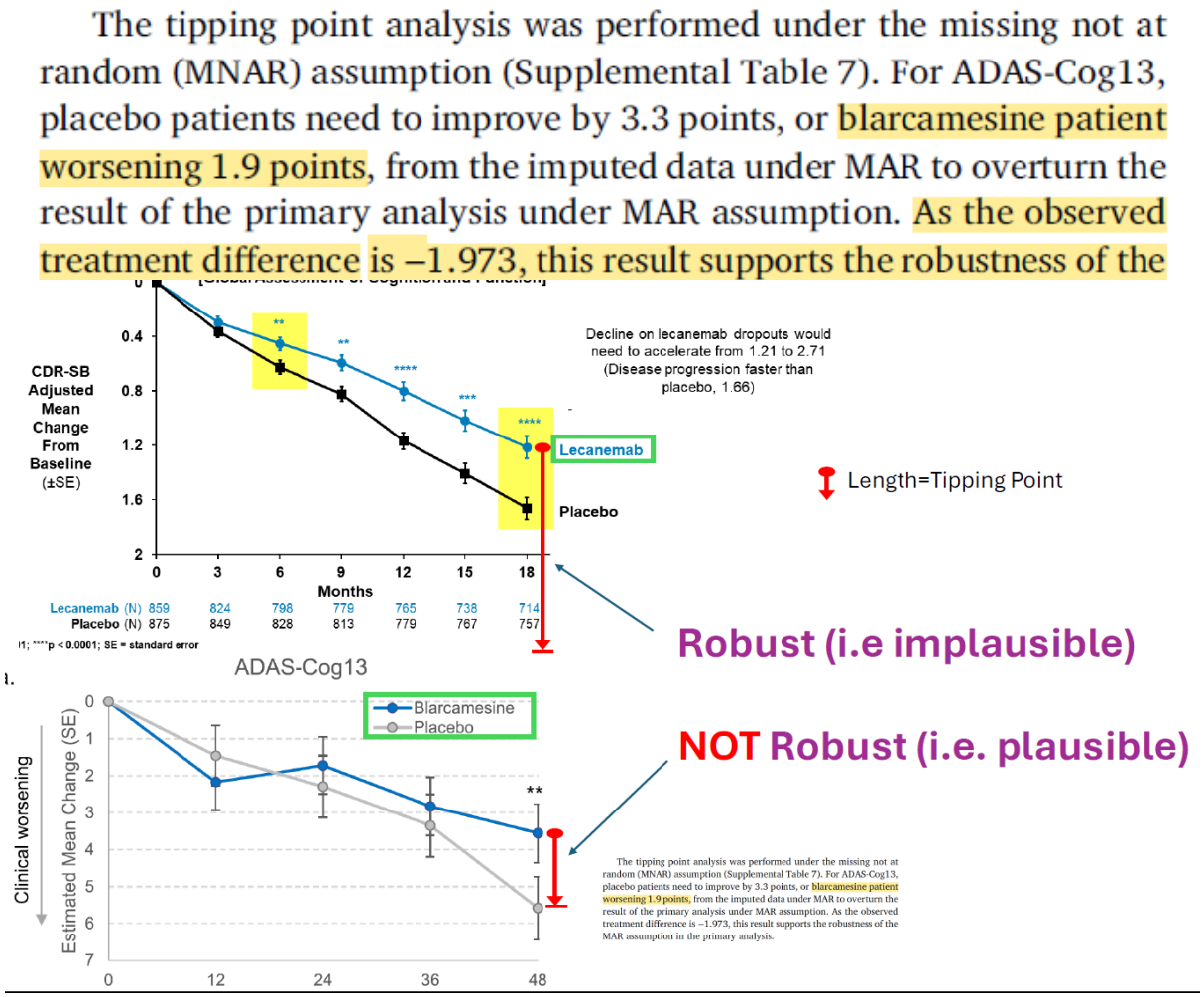
Demographic Characteristics	Blarcamesine 30 mg (*N* = 154)	Blarcamesine 50 mg (*N* = 144)	Blarcamesine Group (*N* = 298)	Placebo (*N* = 164)
MMSE score at baseline, n (%)				
≤ 20	22 (14.3)	21 (14.6)	43 (14.4)	25 (15.2)
>20	132 (85.7)	123 (85.4)	255 (85.6)	139 (84.8)

See: highlighted MMSE score at baseline

Jesse Brodkin, a research scientist who identified clinical inconsistencies in the Cassava Sciences debacle, also notes inconsistencies in Anavex's presentations. The tipping point analysis is also misinterpreted by Anavex; a tipping point analysis is a sensitivity analysis to test how robust a study's findings are to missing data assumptions, it explores how much missing

data would be needed to overturn study conclusions. If it needs an extreme or unrealistic data shift to change the outcome, then the result is considered robust. Suppose a drugs cognitive benefit is +2.0 points on ADAS-Cog13 vs. placebo. A tipping point analysis would show that for the drug to lose stat-sig, placebo patients would have to improve by +5.0 points, which is highly unlikely. This would mean the result is robust because such a placebo improvement is implausible. Anavex claims for their primary analysis to become non stat sig, either placebo patients would have to improve by +3.3 points (unlikely) or Blarcamesine patients would have to worsen by -1.9 points (they argue still better than placebo). They conclude since blarcamesine worsening by 1.9 points would still be better than placebo, the study result is "robust". Anavex misunderstands: The tipping point value is inversely related to the likelihood of the result being overturned. The tipping point (-1.9 points) is clinically plausible. The trial is not robust because a small worsening in Blarcamesine patients could erase the stat-sig. A placebo response of +3.3 is also not impossible.

Because treatment difference was only -1.973 points, a small shift in missing data assumptions could erase significance. If placebo response was slightly higher or if Blarcamesine performed slightly worse in missing patients, the entire study result could be non-statistically significant.



Brodkin also observes that when the clinical trial was first presented at the CTAD conference in 2022, the mean of the placebo group's baseline ADAS-Cog13 score was 29.18. In the current publication, it is reported as 30.4. This is another discrepancy in clinical calculations.

ANAVEX®2-73-AD-004 Primary Endpoint – ADAS-Cog

- **ANAVEX®2-73 treatment slowed cognitive decline by 45% compared to placebo at 48 weeks**
- **Mean difference in ADAS-Cog score change of -1.85 points**

Treatment Group	ADAS-Cog Score, Mean (SE)			Relative Reduction in Decline (%)		
	Baseline	Week 48	Mean Change	Mean	95% CI	P-value
Intent-to-treat (ITT) Population						
Placebo	29.18 (0.61)	33.26 (0.98)	4.11 (0.86)	Ref.	-	-
ANAVEX®2-73	27.62 (0.50)	30.36 (0.83)	2.26 (0.51)	45.02	(43.68, 48.24)	**0.033**

But in the current publication the mean is reported as 30.4

S. Macfarlane, T. Grimmer, K. Teo et al. The Journal of Prevention of Alzheimer's Disease 12 (2025) 100016

Table 1
Demographic characteristics of the Intent-to-Treat (ITT) population.

Demographic Characteristics	Blarcamesine 30 mg (*N* = 154)	Blarcamesine 50 mg (*N* = 144)	Blarcamesine Group (*N* = 298)	Placebo (*N* = 164)
Sex, n (%)				
Female	74 (48.1)	69 (47.9)	143 (48.0)	82 (50.0)
Male	80 (51.9)	75 (52.1)	155 (52.0)	82 (50.0)
Age, Mean (SD)	73.7 (6.6)	74.1 (6.3)	73.9 (6.5)	73.5 (6.3)
Race, n (%)				
Asian	3 (1.9)	4 (2.8)	7 (2.3)	2 (1.2)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)
Other	1 (0.6)	0 (0.0)	1 (0.3)	3 (1.8)
White	150 (97.4)	140 (97.2)	290 (97.3)	157 (95.7)
Ethnicity, n (%)				
Hispanic or Latino/a or of Spanish origin	5 (3.2)	2 (1.4)	7 (2.3)	1 (0.6)
Not Disclosed	7 (4.5)	6 (4.2)	13 (4.4)	8 (4.9)
Not Hispanic or Latino/a or of Spanish origin	142 (92.2)	136 (94.4)	278 (93.3)	155 (94.5)
APOE ε4 genotype, n (%)				
Noncarrier	47 (30.5)	47 (32.6)	94 (31.5)	46 (28.0)
Carrier	99 (64.3)	89 (61.8)	188 (63.1)	106 (64.6)
Heterozygotes	69 (44.8)	65 (45.1)	134 (45.0)	76 (46.3)
Homozygotes	30 (19.5)	24 (16.7)	54 (18.1)	30 (18.3)
Missing	8 (5.2)	8 (5.6)	16 (4.0)	12 (7.3)
Baseline clinical scores, Mean (SD)				
ADAS-COG13 score	28.4 (8.4)	28.9 (9.1)	28.6 (8.7)	30.4 (8.4)
ADCS-ADL score	66.7 (7.4)	67.0 (7.9)	66.9 (7.6)	66.4 (7.1)

Credit to Jesse Brodkin for these observations.

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ANAVEX®2-73-AD-004 Primary Endpoint – ADAS-Cog

- ANAVEX®2-73 treatment slowed cognitive decline by 45% compared to placebo at 48 weeks
- Mean difference in ADAS-Cog score change of -1.85 points

Treatment Group	ADAS-Cog Score, Mean (SE)			Relative Reduction in Decline (%)		
	Baseline	Week 48	Mean Change	Mean	95% CI	P-value
Intent-to-treat (ITT) Population						
Placebo	29.18 (0.61)	33.26 (0.98)	4.11 (0.86)	Ref.	-	-
ANAVEX®2-73	27.62 (0.50)	30.36 (0.83)	2.26 (0.51)	45.02	(43.68, 48.24)	**0.033**

ANAVEX®2-73-AD-004 Baseline Disease Characteristics

	Placebo (n=170)	ANAVEX®2-73 30mg (n=169)	ANAVEX®2-73 50mg (n=169)	ANAVEX®2-73 Total (n=338)
Age, years, mean (SD)	73.4 (6.44)	73.9 (6.76)	73.9 (6.49)	73.7 (6.56)
Female, n (%)	83 (48.8)	83 (49.1)	77 (45.6)	243 (47.8)
Race, White, n (%)	163 (95.9)	165 (97.6)	164 (97.0)	492 (96.9)
Ethnicity Non-Hispanic or Latino or of Spanish origin, n (%)	158 (92.9)	156 (92.3)	160 (94.7)	474 (93.3)
Use of Alzheimer's Disease Medications, n (%)	112 (66.7)	109 (65.3)	109 (64.9)	218 (65.1)
MMSE Score[a], mean (SD)	23.11 (2.69)	23.62 (3.10)	23.52 (2.73)	23.57 (2.92)
ADAS-Cog Total Score[a], mean (SD)	30.25 (8.93)	28.43 (8.52)	29.07 (8.83)	28.75 (8.67)
ADCS-ADL Score[a], mean (SD)	66.48 (7.08)	66.59 (7.26)	66.85 (7.95)	66.72 (7.59)
CDR-SB Total Score[a], mean (SD)	4.10 (1.76)	3.82 (1.65)	3.80 (1.81)	3.81 (1.73)

We can do an unpaired t-test analysis in order to calculate statistical significance, based on some of the data from the slides above. It is important to note that, it seems, Anavex also calculated their 'mean change' incorrectly. 30.36-27.62 is not 2.26, it is 2.74 (Anavex notes it as 2.26, though we will proceed with the correct mean in the t-test).

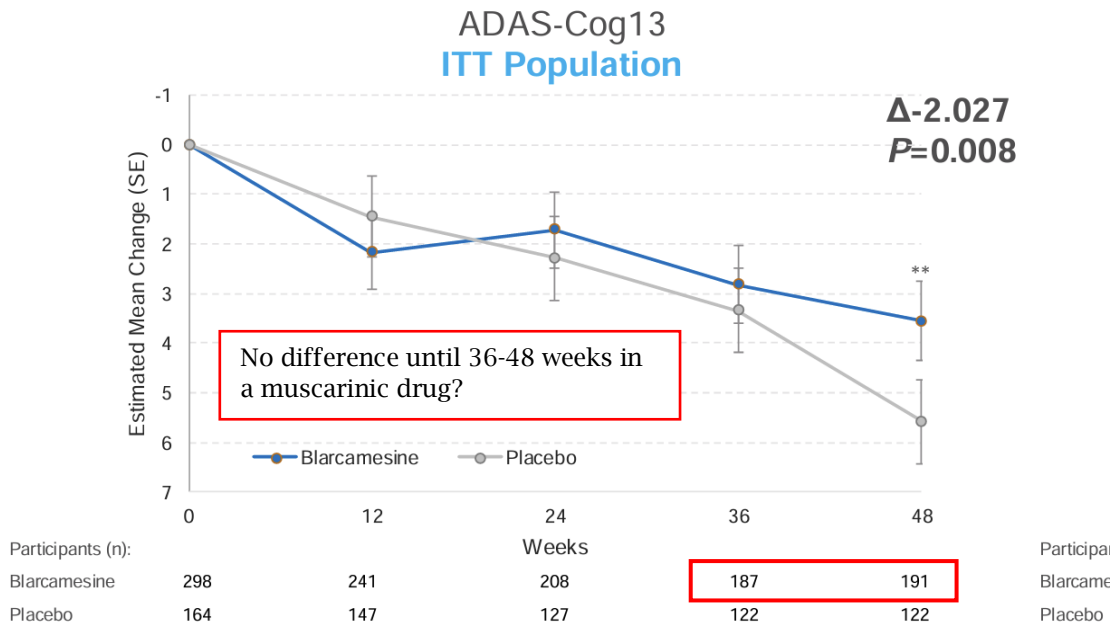
Group	Placebo	Drug
Mean	4.08	2.74
SEM	0.86	0.51
N	170	338

Doing a basic t-test calculation, the P value = 0.1559, which is not statistically significant, t=1.4213.

I also have questions regarding the 48-week separation between blarcamesine and placebo: The drug is supposed to work through a rapidly acting mechanism, but it doesn't separate from placebo until 48 weeks, up until 36 weeks the drug is not statistically significant. A muscarinic should separate right away. Blarcamesine is a muscarinic agonist; muscarinic drugs typically begin demonstrating efficacy within hours, as in the case of Trihexyphenidyl, used for Parkinsons disease: The drug had an onset of action within 1 hour after oral administration. The longest acting muscarinic I have found was Xanomeline-Trospium (KarXT) in clinical trails for schizophrenia, and did not demonstrate significant symptom reduction until 5 weeks; this is still a far cry from blarcamesine's 48-week action onset (Kaul, 2024). More people were also added to the study between 36 weeks and 48 weeks for blarcamesine (red box below), which is highly unusual in clinical trials, if anything, the number of patients should go down due to drop-out. (this could have been enough to separate from placebo and explain the difference at 48 weeks). It is very difficult to uncover a reasonable pharmacological explanation as to why the drug would suddenly work at 48 weeks, and show no statistically significant difference prior to this, even being beaten by placebo up until around 18 weeks.

Disclaimer: The author of this paper is short shares of Anavex Life Sciences (NASDAQ: AVXL)

Coprimary Endpoint: ADAS-Cog13



There are numerous highly irregular processes that have happened during the clinical trials of blarcamesine: Statistical inconsistency in ITT and mITT populations, unusual MMSE inclusions, a misunderstanding of tipping point analysis, differing ADAS-Cog13 scores, incorrect mean calculations, a failed t-test, trial-altering patient inclusion at 48 weeks, and probably the biggest pharmacological mystery, why does the drug, a Muscarinic, suddenly have statistically significant effect at 48 weeks?

Part 3: Anavex Stock, Approval Probability and Conclusion

Currently, Anavex trades for $9/share, down 8% on donanemab rejection news, and down from the year-to-date high of nearly $15/share. There are 84.8 million shares outstanding for a market capitalisation of around $750 million. Coverage of the stock is limited to bucket-shop style analysts, with H.C. Wainwright analyst Raghuram Selvaraju reinforcing his price target of $42/share in February 2025. Institutional owners are limited to index funds (Blackrock, Vanguard, State Street etc) and Quant firms (Susquehanna, Two Sigma, Citadel). The largest apparent institutional long position is from NWAM LLC, an asset manager with $3.2bn AUM. Insiders own 3.04% of the float, and retail owns, unsurprisingly, around 61% of float (slightly below Cassava, where retail owned about 70%!). Typical retail ownership of a company is 13-15%, so 60% retail ownership is significant, and indicates institutions want to stay away. A significant 29% of the float is sold short already. Storied biotech funds, like Baker Brothers, Deerfield, or Orbimed are nowhere to be found amongst Anavex's owners.

Observably, many Anavex retail owners, as is typical in small cap biotechs, know little to nothing about the space, and are holding the stock in an attempt to turn it into a GameStop Esque 'meme stock'. A brief visit to the Anavex reddit page (a forum social network) shows the prevailing retail sentiment. Popular posts such as:

- 'Anavex Life Sciences Short Squeeze Could Melt Faces!'
- 'Anavex will hit 40usd end of January 25!'
- '$AVXL – Alzheimer's Stock Delivering Tendies' (sic)
- 'Big Pharma Fumbles, AVXL Blasts off!'

One may question the point of analysing this retail sentiment, which is reasonable; to answer, I say it is important to analyse how 'cult-like' a stock becomes, as it can be an incredible indicator of failure, especially in biotech. Anavex, like Cassava, has die-hard defenders and stock pumpers, who treat the stock, functionally, as a lottery ticket.

On Probability

I believe chances of blarcamesine receiving EMA approval are low, but how low? I quantify this using a drivers-based probability approach.

Factor	Probability after Adjustment	Penalty Applied	Notes
Base Rate for AD Drug Approval by EMA	5% (baseline probability)	Nil	A generous assessment of an Alzheimer's drug beating phase III trials and making it to market (2/100 succeed in reality).
Only one pivotal trial with no replication	15%	-5%	EMA typically requires >2 studies unless effect size is large and unequivocal (which it isn't)
Failed co-primary endpoint ADCS-ADL	7.5%	-6.5%	EMA prizes function in their approval guidance
Modest effect size and dropout imbalance	4.5%	-3%	Stat sig but barely clinically relevant, 35% dropout in treatment arm
Data integrity issues	4.5%	-1%	Reduces EMA confidence in protocol adherence
Donanemab EMA rejection	3.5%	-1%	Donanemab had much more comprehensive studies, similar cognitive benefits, and was ultimately rejected by EMA.

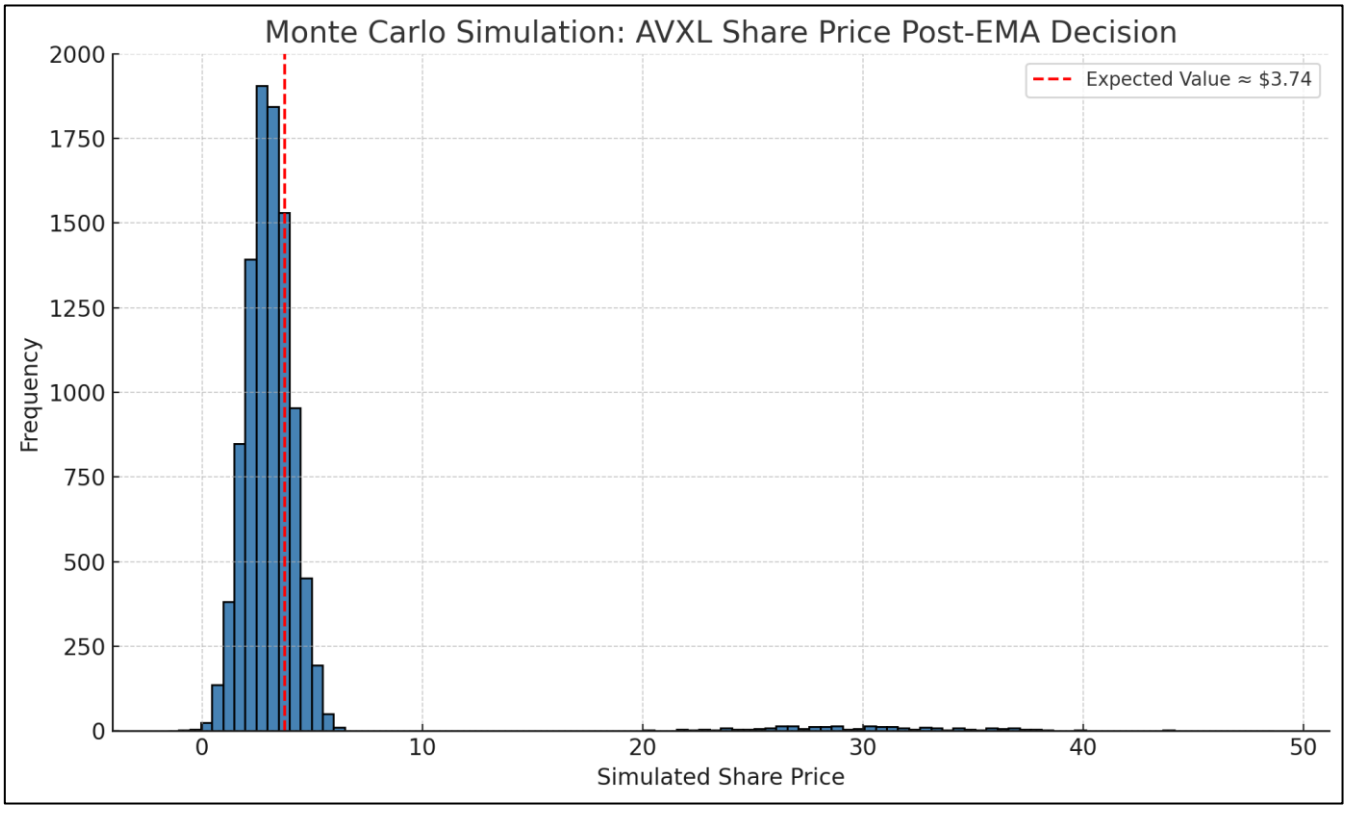
Ultimately, I estimate the probability of EMA approval to be 2.5-3.5%, whilst EMA rejection is at 97.5-96.5% of occurring. If approval was to occur, the relative valuation of Anavex should near-instantaneously move to at least $3bn, a 304% increase, and is more likely to reach double-digit billions, representing stock price an order of magnitude higher than current price. On rejection, Anavex should trade around $2-3/share, near cash value, also valuing the other drugs in its pipeline.

To determine the market implied probability, we can look at October options pricing and calculate with basic math from there:

Input	Value
Approval Price	$30
Rejection Price	$3
Current Price	$8.72
$10 Call Ask	$2.25
$10 Put Ask	$3.50

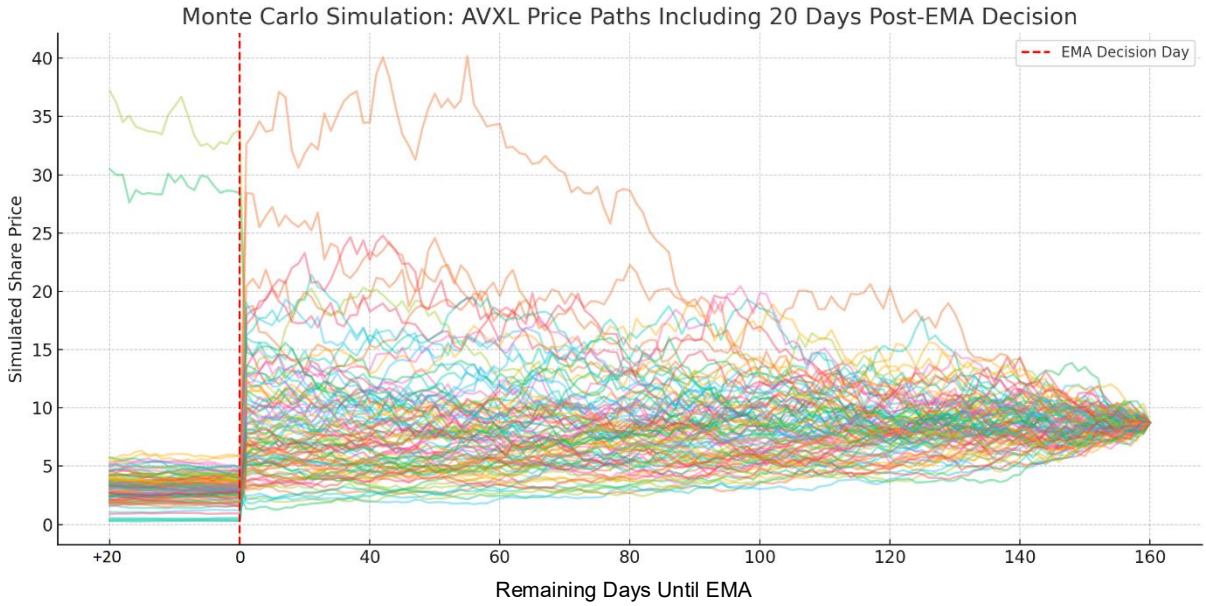
The call premium works out to 11.25%, while the put premium works out to 50%, with the market implied approval average probability being 30.6%. This is a significant disconnect from our previous 2.5-3.5% estimation. October 2025 options also skew heavily towards puts; the put-call skew assigns a material probability that AVXL crashes in late 2025, but still significantly less than the probability I assign. We can also run a monte carlo simulation to estimate expected valuation across thousands of scenarios.

The Monte Carlo Simulations

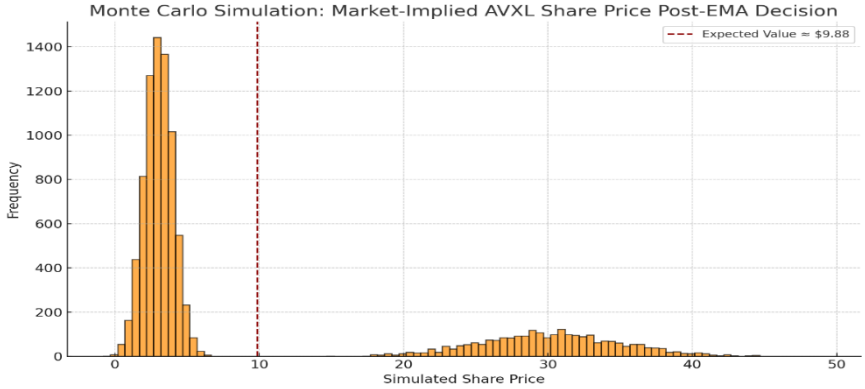


As we can observe, the expected valuation based on this simulation is around $3.74, accounting for risk of approval. I input an approval probability of 2.5%, mean approval valuation of $30 with a standard

deviation of $5, and a mean rejection valuation of $3 with a standard deviation of $1. 10,000+ simulations were run to generate this chart, and the simulation suggests the stock is around 130% overvalued (relative to true value, not current price). The histogram shows a tight frequency cluster around the $3 mark, and very few scenarios that result in approval.



These are some of the simulated price paths the simulation took, with volatility and drift until the EMA decision; 0-day represents the binary event of EMA approval/denial. I incorporated stochastic drift, simulating the daily price path using a standard Geometric Brownian Motion. The overwhelming majority of price paths end up around the $3 range, while very few result in actual approval-based valuations. This graph communicates the incredibly skewed payout structure of the trade.



This is the market implied monte-carlo; as we can see, there is a significant disconnect between our internally estimated model and the market implied model. The EV of AVXL shares for this simulation are around $9.88, about 165% higher than our estimated EV of $3.74/share.

Conclusion

The author of this paper is short shares of Anavex Life Sciences due the anticipated rejection of the company's drug candidate, blarcamesine, by the EMA. The market is significantly overestimating odds of approval, and an asymmetric opportunity exists to short. Anavex's days of a near-billion-dollar market capitalisation is numbered and blarcamesine will be rejected by year-end 2025.

Legal Disclaimer

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