Anavex Life Sciences: Dizzying Expectations of a Drug That Doesn't Work

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October 6, 2025

Abstract

Anavex Life Sciences (NASDAQ: $AVXL) is a pre-revenue biopharmaceutacal company pursuing EMA approval for their lead drug candidate, blarcamesine, which is a small-molecule Sigma-1 receptor agonist, for the treatment of early Alzheimer's disease (AD). Blarcamesine has limited efficacy, significant treatment-emergent adverse events, a failed phase IIb/III trial, and a developer with a track record of deceit, spin and manipulation. This drug will not receive EMA approval. After a negative recommendation against approval from the CHMP, Anavex stock will likely see a 50+% decline in its share price.

Contents

1 Overview

Anavex Life Sciences ($AVXL) is a pre-commercial biotech company pursuing a platform of central nervous system (CNS) therapeutics. Its primary drug candidate is blarcamesine [1] (also known as ANAVEX2-73), a Sigma-1 agonist that the company is currently trying to gain European Union approval for use in early Alzeimer's disease (AD). The drug has questionable efficacy: its phase III trial failed one of its two co-primary endpoints, whilst the successful co-primary endpoint only showed separation with the placebo group at the end of 48 weeks [2]. The trial also showed serious adverse events (AEs) in the therapeutic population. Over 1/3 of patients in the drug group experienced dizziness, compared to 6% in the placebo group, and 14% of patients in the drug group experiencing a confusional state, compared to 0.6% in the placebo group [2].

The unacceptable adverse events, poor efficacy and untrustworthy past behaviour of management mean that the European Medicines Agency (EMA) must reject blarcamesine as a treatment for Alzeimer's disease.

Anavex also has a Schizophrenia drug candidate, ANAVEX 3-71, which recently had a read-out of its phase II trial [3]. This is a different molecule to blarcamesine. However, its mechanism of action is also Sigma-1 receptor agonism with M1 muscarinic positive allosteric modulation (PAM). The 'successful' primary endpoint of the Schizophrenia trial was reaching safety and tolerability, not efficacy. The schizophrenia programme is a zero as discussed in Sec. 2.6.

The key negative catalyst for Anavex's share price will be a recommendation against blarcamesine approval from the Committee for Medicinal Products for Human Use (CHMP). At their September meeting (Sept. 15th-18th), the CHMP sent Anavex management a Letter of Outstanding Issues (LoOI). The standard time to respond to this is 4-6 weeks. After a response, the CHMP will have 30 days to make their final recommendation, which will be published in the highlights of one of their upcoming meetings. The remaining meeting dates in 2025 are: Oct 13th-16th, Nov 10th-13th and Dec 8th-11th.

2 Shady Business

2.1 Company History and Dilutive Financing

Anavex was founded in January 2004 as Thrifty Printing, by Wu Yang and Wu Pei Ru, their prospectus summary stating: "We are an on-line photofinishing company" [4].

Three years later, the company re-branded as Anavex Life Sciences, appointing Dr. Panos Kontzalis as CEO [5], and acquired the rights to a patent portfolio of Central Nervous System drug candidates from Dr. Alexandre Vamvakides, who was made Chief Science Officer [6]. A remarkable pivot, from printing birthday cards, to curing Alzheimer's Disease[1]. CEO Chris Missling, PhD, was appointed CEO in 2013 [7]. In the same press-release, the company announced it had entered into its first vulture funding agreement with Lincoln Park Capital.

2.1.1 Dilutive Financing

The company's stock continued to trade on the OTC market - excluding a 2013 trading halt by the British Colombian Securities commission - until it was up-listed to trade on the NASDAQ in 2015 [8]. Before and after the up-listing, the company was engaged in rampant paid stock promotion which was subject to a class action court case in 2016 [9].

All funding has come from either issuing equity or small research grants (from the likes of the Michael J. Fox foundation) and thus common shareholders have experienced high levels of share dilution throughout the

[1] I note that it is not uncommon for new companies to adopt the shell of dormant publically listed corporations to gain access to public equity markets, without having to go through a costly IPO.

company's history. Dilution has been especially value-destructive due to the long-standing vulture funding arrangement between Anavex and Lincoln Park Capital. Starting in 2013, the agreement allowed Anavex to sell shares at variable below-market prices, often with built-in discounts, giving Lincoln Park a risk free profit and granting management easy cash to pay themselves hefty salaries. A $10MM Lincoln Park Capital agreement in 2013 was followed by a $50MM agreement in 2015 and a $150MM agreement in 2023 [10].

Their most recent fundraising efforts are a $150MM shelf offering, filed on the 25th of July 2025 [11]. Highlighting management's lack of transparency, this $150MM offering was not disclosed as a subsequent event in their Q3 earnings press release or conference call (12th of August 2025), despite highlighting their latest blarcamesine findings (dated 31st of July 2025) and a conference appearance (27th July 2025) which both occured *after* the offering[2]. [12] [13]

The equity agreements with Lincoln Park Capital and other firms [14] have resulted in heavy share dilution: from 2015 to 2025, the number of shares outstanding has increased from **34MM to 85MM** shares.

To give management credit, they have at least stayed true to their original mission; only instead of printing photographs, they now print shares.

2.2 Executive Compensation

Figure 1. CEO, Christopher Missling [15]

In his position as CEO, Missling has been awarded substantial compensation. Missling receives a base salary of $800k [16] and a total compensation package of $6.8MM in 2022, $3.9MM in 2023 and $2.8 in 2024 [17]. Missling's compensation package is primarily in stock options and the apparent decrease in total compensation is because from 2022 to mid-2024, Missling oversaw a share drop of over 80%. As of his most recent filing, Missling owns 1,510,165 shares [18]. There are currently 85,893,834 shares outstanding [10] and, via stock-based compensation, Missling now owns 1.758% of all shares outstanding. Including all in-the-money options that Missling has been awarded and has yet exercised, Missling is in control of ~ 7 million shares, more than 8.1% of all outstanding shares.

In exchange for his hefty compensation, the company have in the past set milestones that do not correlate to shareholder value-creation. We can see this from the targets set out in Missling's 2022 employment agreement [19]:

- *Completion of ANAVEX2-73-AD-004 Phase 2b/3 study in Alzheimer's disease*
- *Initiation of ANAVEX2-73 imaging-focused Parkinson's disease clinical trial*

[2]It should be noted that disclosing subsequent events outside of the quarter in the the earnings call is not an SEC requirement.

- *Initiation of ANAVEX2-73 Phase 2/3 Fragile X clinical trial*

As noted by other commentators [20], these milestones are for completing or starting clinical trials - not for achieving regulatory approvals or drug sales. Management is funneling millions of dollars per year from shareholders to insiders and in exchange they do not have to accomplish anything that provides real value.

2.3 Part-time CFO

How many $800+MM market cap companies employ a part-time CFO? Sandra Boenisch has allegedly operating as the Principal Financial Officer and treasurer of Anavex since 2015 according to company filings [17]. However, instead of being employed as a full time CFO by the company, she was an independent consultant working full-time at her company Assent Advisory Partners [21]. She has also never had experience of managing a large publicly traded company before her Anavex appointment. Yet, at Anavex she enjoys total compensation of $400-500k per year [17].

Outside of Anavex's SEC filings, there is virtually no public record of Boesnisch. If it wasn't for a nine year old short report [21] and Boenisch's cross-fit profile [22] there would have been serious doubts on whether the CFO ever existed. With a CFO like this, perhaps it should be obvious why the company has had such an exotic history raising money (see sec. 2.1.1).

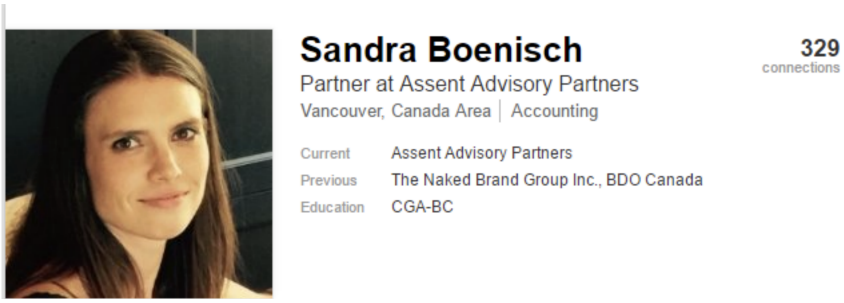


Figure 2. Screenshot of Principal Financial Officer, Sandra Boenish's LinkedIn ∼ 2016, when she was allegedly employed as by Anavex, showing her to actually be working for Assent Advisory Partners.

2.3.1 Mom, management is writing papers again!

In defense of Missling, he does seem to engage with the research activities of the company. It is not inherently a red-flag for the CEO of a company to co-author clinical research papers. But when Chris Missling manages to shoe-horn his name onto seemingly *every* publication that Anavex pushes out [23], it is forgivable to read the papers through a more critical lens. The 2025 paper discussing the results of the blarcamesine phase IIb/III AD trial [2] is questionable reading (see Fig. 8a).

2.4 Stock Price Manipulation Allegations

Anavex Life Sciences has received several allegations of stock price manipulation. There are three outstanding investor class actions against the company [24].

A particularly damning class action was filed in 2016 due to the company's alleged programme of stock price manipulation from 2013-2015, during which Anavex shares were up-listed from the OTC markets to the NASDAQ [9]. Anavex is nearly entirely reliant on equity financing to fund their continued operation and to maintain the lofty compensation of company executives, and so there is obvious motivation to reach elevated stock prices in order to dump shares on hype-driven retail investors. As a result of a consistent campaign

(a) CEO, Christopher Missling, partying with models [21]

(b) CFO, Sandra Boenisch 'pumping and dumping' iron (there are just two images of her in existence). [22]

Figure 3. The highly paid Anavex Life Sciences executive team

of paid stock promotion in tandem with hyped press releases, the stock surged over 1,500% in 2015, rising from $0.65 per share in late 2014 to $14+ by late 2015. The plaintiffs in the 2016 case alleged that the campaign included bulletins, videos, newsletters, and reports from third-party publishers, and that these releases were timed to align with significant equity financing events, including when $AVXL was up-listed to the NASDAQ. Incredibly, one stock pumper, who went by the name "Dr Kanak Kanti De" was paid to publish at least 16 reports: these included interviews with CEO Chris Missling and Anavex's clinical trial director. Hilariously, it was later discovered by that Kanti De was not even a real medical doctor (see Feuerstein's tweet in Fig. 4c).

At no point in time did management disclose that they were behind the paid promotional material published about Anavex stock. Even more troubling, they allegedly purposefully obfuscated the expense in their company reports,"[removing] investor relation fees as a line item in the company's expense tables and eventually provided no information at all about these fees." [9].

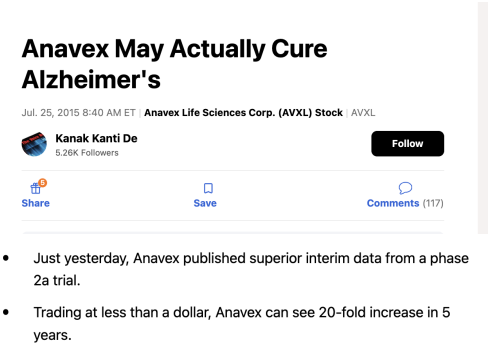
Unfortunately, the court eventually dismissed the case, determining that the plaintiffs did not prove strong enough intent to deceive. However, the evidence brought up in the trial is clear enough to question the ethics of Anavex management.

2.5 Delayed and Misrepresented Results

In their 2022 AVATAR Rett syndrome study (also blarcamesine), management changed the efficacy endpoints just weeks before the trial results were announced [28]. They decided to ditch the standard RSBQ and CGI-I measures for a Anavex-exclusive "drug exposure-dependent" responder analysis. Unsurprisingly, using a fake efficacy measure, Anavex was able to announce that the trail was a success, stating that 72% of participants "responded" to blarcamesine, versus a placebo response rate of 38% [29].

The Rett programme was continued with a further study called EXCELLENCE. This was a failure. Normally, it should take a drug company 6-8 weeks to publish results after completion, however, results of the Rett EXCELLENCE study were inexplicability delayed for 7 months. So, it should be obvious how hard management tried to find *any* spin they could employ on the failed results [30].

(a) Serial pumper of bioturds, 'Dr' Kanak Kanti De. [25]



(b) S**king alpha article from Kanti De, pumping $AVXL in 2015 [26].

(c) Feuerstein tweet exposing Kanti De [27]

Figure 4. $AVXL has been riddled with stock manipulation schemes for decades.

After such an *incredible* performance in the AVATAR and EXCELLENCE studies, where is their blarcamesine for Rett syndrome programme now? Dead [31].

Or at least to any reasonable person, this programme would be dead, but management decided to blame a "large placebo effect" for the EXCELLENCE failure and has not yet officially axed the programme. It is left as an exercise for the reader to determine why management would want to keep the zombie Rett programme alive (see Sec. 2.2 on executive compensation).

2.6 Failed Spin of Schizophrenia Data

Recently, Anavex published a press release announcing that their Schizophrenia trial succeeded [3]. The primary endpoint for this **phase II** trial was "demonstrating that ANAVEX®3-71 was safe and well-tolerated". A phase II trial is supposed to judge a drug's efficacy, answering the question, "Does Drug X improve Disease Y?" [32]. Under Anavex's approach, one could take a sugar pill to phase II trials and successfully readout that it was "safe and well-tolerated".

In the absence of releasing hard data, the company stated: "secondary and exploratory analyses revealed encouraging trends in several outcome measures". That doesn't scream confidence that the drug shows efficacy in treating Schizophrenia, if it did, one would logically assume they would release efficacy data.

This a deeply unserious platform for the treatment of Schizophrenia. The pessimist in me sees this press release as a last gasp stock pump (allowing management to hit the $150MM ATM offering) before the inevitable rejection of blarcamesine.

2.7 A Note on Analyst Coverage and Institutional Ownership

The reader may question why such an obvious zero like $AVXL would be given lofty price targets by analysts (e.g. $42 by H.C. Wainwright [33], $46 by D. Boral Capital [34]). The analysts base their valuations off hypothetical post-approval drug sales but their true intentions stem from the fact that their firms are often directly involved in share offerings, earning commissions in the millions of dollars. In Anavex's $50MM share offering in June 2021, H.C. Wainwright & Co. acted as the exclusive placement agent and generated around $3MM for their services [14] [35].

Institutional ownership of $AVXL sits at around 38% [36]. This is almost entirely passively managed index funds (that are forced to buy bottom of the barrel companies that happen to be in the tracked index) or quant/market maker funds. Smart money and biotech funds are not buying this name in size - the majority of $AVXL is owned by retail investors and insiders (who receive shares for free as part of their compensation).

3 Blarcamesine

3.1 History of the Drug

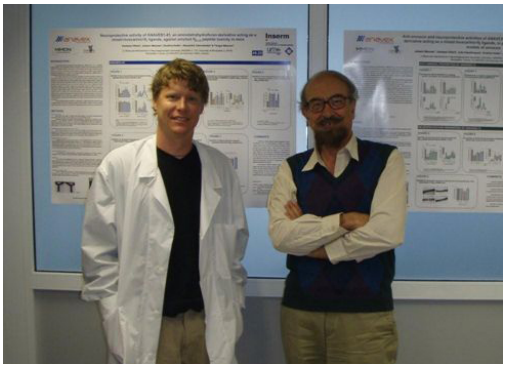


Figure 5. The only known publicly available photograph of Dr. Alexandre Vamvakides (right), alongside stock pumper Brian Hicks[3], $\sim$ 2008. [37]

Blarcamesine is the flagship product of Anavex Life Sciences. It was discovered by Dr Alexandre Vamvakides in the 1990s [39] and Anavex was assigned the patent in 2007, alongside Vamkides being appointed as Chief Science Officer.

The drug went through phase IIa clinical trials from December 2014 until September 2015 [40]. In the publication of the phase IIa clinical trial, the results only showed the drug worked in a subgroup. The phase IIb/III trial was then ran from August 2018 until June 2022, targeting a broad patient population, a curious change of tack by management. If the drug was shown to work effectively for a genetic subgroup, why not stratify for and only target that subgroup in the phase IIb/III?

In contrast to phase III trials for successfully approved AD treatments like Biogen's lecanemab-irmb (78 weeks placebo-controlled) [41] and Eli Lilly's donanemab (76 weeks placebo-controlled) [42], the blarcamesine phase IIb/III trial was only carried out for 48 weeks, with a 96 week *non-placebo-controlled* open-label extension. The severely limits the ability of the phase IIb/III study to show efficacy of blarcamesine for AD, which is a disease where we look for a slowing disease progression over a long period of time.

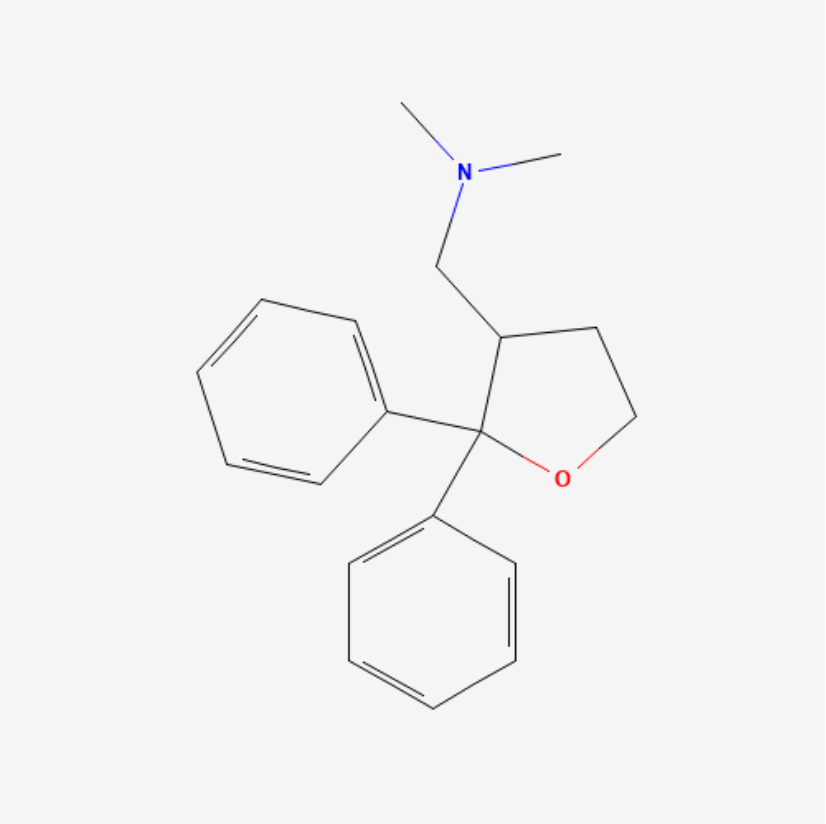


Figure 6. The Blarcamesine molecule.

3.2 Mechanism of Action

Alzheimer's disease is primarily caused by the buildup of amyloid and tau proteins in neurons, leading to neurodegeneration, brain shrinkage, and cognitive decline. Age is the main risk factor, while genetics, lifestyle, neural inflammation, and oxidative stress also contribute to disease progression.

Anavex's early preclinical work, initiated around 2010–2012, is claimed to demonstrate blarcamesine's ability to enhance autophagy, reduce neuroinflammation, and improve synaptic plasticity in cellular and animal models of neurodegeneration. In a simple sense, blarcamesine is claimed to activate an upstream, internal cell pathway that helps clear protein aggregates inside cells.

3.2.1 Target Proteins: Sigma-1 and Muscarinic M1

The primary target of blarcamesine is the Sigma-1 receptor (σ_1). This is a chaperone protein that helps correctly fold proteins inside cells and modulates calcium ion exchange between the endoplasmic reticulum (ER) and mitochondria. In a healthy cell, σ_1 is inactive and is bound to the binding immunoglobulin protein (BIP). Under cell stress conditions (ER stress due to misfolded protein build-up, metabolic stress, oxidative stress or excitoxic stress), σ_1 dissociates and becomes active, modulating downstream protective pathways.

When activated, σ_1 stabilises inositol trisphosphate (IP_3) receptors at the ER. This promotes proper calcium release from ER to the mitochondria, driving ATP production, and causing neurons to have more energy

[3]Although the dates don't exactly align, it is possible that this is the same Brian Hicks who was convicted of securities fraud in 2006 [38]. Hicks did not respond when approached for comment.

for signaling and repair. The calcium regulation and interaction with mitochondrial proteins reduces mitochondrial stress. Mitochondrial dysfunction will often lead to increasing production of free radicals/reactive oxygen species inside cells, which can directly lead to neuro-degeneration. The activation of σ_1 can help neurons survive longer under diseases like AD. When the cell is stressed (like with the buildup of mis-folded proteins), σ_1 activates and helps proteins fold correctly and regulates the unfolded protein response. Hence, σ_1 acts to prevent build-up of amyloid and tau proteins.

The molecule also binds less selectively to the Muscarinic M1 receptor. Activation of M1 signaling enhances cholinergic transmission, boosting excitatory neurotransmission in the cortex and hippocampus. It improves synaptic plasticity by facilitating long-term potentiation in hippocampal neurons and strengthening synaptic connections, a critical process for memory formation. M1 activation also triggers neuroprotective intracellular cascades, such as PI3K/Akt and MAPK/ERK, promoting neuronal survival and resilience against stress. There is partial evidence that it may reduce neuroinflammation by dampening microglial activation, while also helping to balance excitation and inhibition in cortical circuits, ultimately supporting cognitive processing.

3.2.2 Plausible Mechanism of Action

In providing further arguments towards the importance of σ_1, management claims that σ_1 expression increases with age in healthy adults and decreases in age in AD patients [43]. They also claim that the decrease in σ_1 expression during AD coincides with an age-related decrease in autophagy. It is then assumed that σ_1 agonism would ameliorate AD.

However, that assumption is not sound biology and is not proven based on the results that have been published. I emphasise: just because the *ablation* of a protein correlates with an *effect*, you can not assume that the *agonism* of the protein will cause the *reverse effect*.

I remind the reader that this was the same faulty logic employed by Atyr Pharma in their Efzofitimod failure: NRP2 ablation correlated with worsening inflammation, however, agonising the NRP2 protein did not reduce inflammation.

The proposed mechanism of action that blarcamesine is able to activate σ_1 and trigger the protective downstream pathways that can slow neuro-degeneration and help AD patients is *plausible*, however, **without strong clinical efficacy and safety data, a plausible mechanism of action means nothing**.

4 Trial Results and CHMP Decision

"Data dredging, also known as p-hacking or data snooping, is the flawed statistical practice of analyzing data in many ways without a prior hypothesis, then only reporting findings that appear statistically significant ($p < 0.05$). This increases the risk of false positives—finding patterns that are due to chance rather than a real underlying effect."

- If only someone would inform Dr. Missling...

4.1 Phase IIb/III Clinical Trial Results Overview

The results of the phase IIb/III blarcamesine Alzheimer's Disease trial were published in early 2025 [2]. To gain understanding of the questionable statistical analysis carried out in the blarcamesine paper, the reader should also explore the writing of other commentators who have explored the trial results in great detail, especially [44].

In the trial, the two co-primary outcomes were:

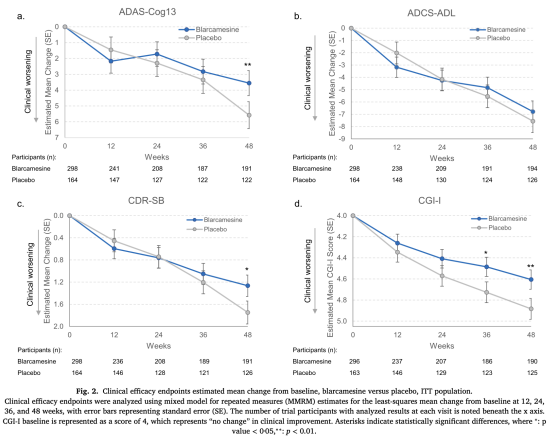


Fig. 2. Clinical efficacy endpoints estimated mean change from baseline, blarcamesine versus placebo, ITT population.
Clinical efficacy endpoints were analyzed using mixed model for repeated measures (MMRM) estimates for the least-squares mean change from baseline at 12, 24, 36, and 48 weeks, with error bars representing standard error (SE). The number of trial participants with analyzed results at each visit is noted beneath the x axis. CGI-I baseline is represented as a score of 4, which represents "no change" in clinical improvement. Asterisks indicate statistically significant differences, where *: p value < 0·05,**: $p < 0.01$.

(a) Endpoint measurements over time

Table 2
Primary and secondary endpoints, Intent-to-Treat (ITT) population.

	Individual Group Comparison			Group Comparison	
	Blarcamesine 30 mg ($N = 154$)	Blarcamesine 50 mg ($N = 144$)	Placebo ($N = 164$)	Blarcamesine ($N = 298$)	Placebo ($N = 164$)
Primary efficacy endpoints					
Change from baseline to week 48 in the **ADAS-Cog13** score					
No. of participants at week 48	108	83	122	191	122
Adjusted mean change	3.650	3.436	5.584	3.555	5.582
Adjusted mean difference vs. placebo (95% CI)	−1.934 (−3.639 to −0.228)	−2.149 (−3.979 to −0.319)	..	−2.027 (−3.522 to −0.533)	..
P value vs. placebo	0.026*	0.021*	..	0.008**	..
Less decline, %	34.6%	38.5%	..	36.3%	..
Change from baseline to week 48 in the **ADCS-ADL** score					
No. of participants at week 48	109	85	126	194	126
Adjusted mean change	−6.702	−6.940	−7.592	−6.785	−7.560
Adjusted mean difference vs. placebo (95% CI)	0.890 (−0.992 to 2.772)	0.652 (−1.370 to 2.673)	..	0.775 (−0.874 to 2.423)	..
P value vs. placebo	0.354	0.527	..	0.357	..
Less decline, %	11.7%	8.6%	..	10.3%	..
Secondary efficacy endpoint					
Change from baseline to week 48 in the **CDR-SB** score					
No. of participants at week 48	107	84	126	191	126
Adjusted mean change	1.253	1.290	1.755	1.266	1.749
Adjusted mean difference vs. placebo (95% CI)	−0.502 (−0.924 to −0.080)	−0.465 (−0.918 to −0.012)	..	−0.483 (−0.853 to −0.114)	..
P value vs. placebo	0.020*	0.045*	..	0.010*	..
Less decline, %	28.6%	26.5%	..	27.6%	..
Exploratory endpoint					
Improvement from baseline to week 48 in the **CGI-I** score					
No. of participants at week 48	107	83	125	190	125
Adjusted improvement	4.634	4.568	4.882	4.606	4.883
Adjusted mean difference vs. placebo (95% CI)	−0.248 (−0.464 to −0.033)	−0.314 (−0.545 to −0.082)	..	−0.278 (−0.466 to −0.089)	..
P value vs. placebo	0.024*	0.008**	..	0.004**	..
Less decline, %	5.1%	6.4%	..	5.7%	..

(b) Endpoint results table

Figure 7. Results of the Phase IIb/III blarcamesine trial

- Reduction in cognitive decline assessed from baseline over 48 weeks with blarcamesine compared to placebo using the 13-item Alzheimer Disease Assessment Scale- Cognition(ADAS-Cog13).
- Reduction in decline of the ability to perform daily activities assessed from baseline over 48 weeks with blarcamesine compared to placebo using the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) Scale.

The endpoint results table for the trial are shown in Fig. 7b. The trial successfully achieved the ADAS-Cog13 endpoint, with an adjusted mean decline from baseline of 3.555 for the drug group and a decline of 5.582 for the placebo group. The adjusted mean difference vs. placebo was −2.027 with a 95% confidence interval (CI) of (-3.522 to -0.533) with a p-value of 0.008. The curious progression of the drug group across clinical visits draws attention. The drug group unperformed at the first data point, on week 12 - supposedly due to negative effects of the titration of the drug up to the target dose. On weeks 24 and 36 there is no statistically significant improvement over placebo. Then, the large divergence occurs only at week 48 - conveniently the endpoint measurement date. Another point of suspicion is the participant numbers in the drug group increasing from n=187 at week 36 to n=191 at week 48, reversing the previous constant decline in participant numbers across measurement dates.

The second primary endpoint, ADCS-ADL, failed. The change from baseline was -6.785 for the drug group and -7.560 for the placebo group. The adjusted mean difference vs. placebo was 0.775 with a 95% confidence interval (CI) crossing zero (-0.874 to 2.423), and a p-value of 0.357.

In Fig. 8b, we can see that the CHMP's own guidelines state that an approved AD treatment must have shown efficacy in **both cognitive and functional endpoints** [45]. In the discussion of the Phase IIb/III blarcamesine clinical trial, the authors believe the trial should be "considered a win" (Fig. 8a). However, the trial did not achieve both of its co-primary endpoints - in no uncertain terms: **the trial failed to show blarcamesine was effective at treating Alzheimer's Disease**.

4.2 P-hacking

The EMA requires studies that contain multiple primary endpoints to have lower p-value thresholds for the results to be considered significant. This is because additional endpoints inflate the familywise type I error rate (i.e. getting a false-positive result). Guidelines do not require a specific p-value, but the method and rationale of the adjustment must be *pre-specified* in the study protocol [45] [46]. A typical approach like the

Discussion

In this Phase IIb/III randomized clinical trial, blarcamesine significantly slowed clinical progression at 48 weeks in the ITT population of participants with early AD for the cognitive primary endpoint ADAS-Cog13 and for the composite cognitive/functional secondary endpoint CDR-SB, while the co-primary endpoint ADCS-ADL did not reach statistical significance at Week 48. The co-primary outcome was met under the multiplicity control rule, since the differences in the least-squares mean (LSM) change from baseline to 48 weeks between the prespecified blarcamesine and placebo groups for ADAS-Cog13 was significant at a level of $P < 0.025$ and for CDR-SB was significant at a level of $P < 0.025$. In addition, current regulatory guidance from the FDA suggests that a sole cognitive endpoint is sufficient for demonstrating significance in early AD study populations [38]. In keeping with current regulatory practice, blarcamesine met the primary endpoint and should be considered a win as measured by ADAS-Cog13 at Week 48. The clinical effect of blarcamesine was supported by two independent biomarkers: a significant increase in pathological amyloid beta levels in plasma, representing a decrease in pathological amyloid beta in the brain, as well as a significant slowing in the rate of pathological brain atrophy in the brain as measured by MRI. Improvement in plasma

(a) Part of the discussion from the blarcamesine phase IIb/III trial results paper, 2025.

8.2.1. Efficacy endpoints in AD Dementia

For patients with **established** AD dementia, efficacy should be assessed in the following domains:

1) cognition, as measured by objective tests (cognitive endpoint);

2) (instrumental) activities of daily living (functional endpoint);

3) overall clinical response, as reflected by global assessment (global endpoint).

Efficacy variables should be specified for each of the three domains.

In mild to moderate AD to accept an effect on cognition it should be clinically meaningful. The clinical relevance should be confirmed by an effect on function or clinical global assessment in a co-primary endpoint approach.

(b) EMA Guidelines on AD medicines

Figure 8. Management spin meets EMA reality.

Bonferroni method, would entail evenly splitting the pre-specified threshold for statistical significance, α, such that each co-primary endpoint should reach $p < 0.025$, leaving the familywise type I error rate < 0.05.

When management looked at the data, I believe they noticed a glaring issue: taken separately, the only successful co-primary endpoint, ADAS-Cog13, hit $p = 0.026$ for the 30mg and $p = 0.021$ for the 50mg group. However, if they were to look at the combined drug group as a whole, the p-value drops to just $p = 0.008$. This is perhaps the most likely explanation for why in the final paper on the trial, the strange decision to pool the 30mg and 50mg dose groups was made.

Management instead claim: "Due to the prespecified flexible dosing design of the study, the 30mg and 50mg assigned dosage arms reached quite similar average cumulative exposure at each study visit; hence the combined blarcamesine group vs placebo is the primary analysis and supported by the comparison of separated dose groups vs placebo." I posit that the EMA will not agree with this. Any pooling decisions would normally be made in the trial design and in the absence of a publicly available study protocol and statistical analysis plan, we have no choice but to decide that this decision was made entirely post-hoc and thus will be scrutinised intensely by the regulators.

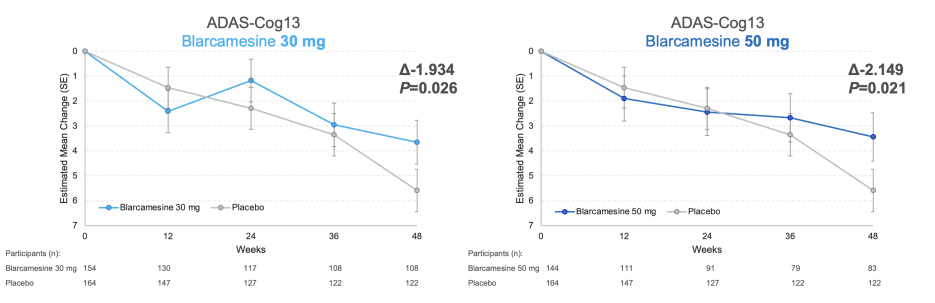
4.3 Lack of Dose Response

Management's decision to pool the blarcamesine dosage data into a single group serves to obscure the dose response of the drug between the 30mg and 50mg doses. Using per-dose data presented by management in [47], alongside accumulated dose exposure for each treatment group at each data point as shown in the supplementary table from [2] (see Fig. 9), I have charted the relationship between the improvement on placebo against the accumulated dose, shown in Fig. 10.

The accumulated dose relationship with the co-primary endpoint ADAS-Cog13 does not show a convincing dose response. The first two measurements, at weeks 12 and 24, both show a *worse result* with increasing accumulated dose of the drug. It is only at weeks 36 and 48 that a higher accumulated dose corresponds to a better improvement on placebo. I believe the regulators will question this relationship and will perhaps require further clinical data to conclusively show efficacy and to determine the most effective dosage.

4.4 Adverse Events and Patient Dropouts

The adverse events in this trial (as shown in Fig. 11) will be the most concerning aspect for regulators and will weigh heavily against approval when judging the risk/benefit of blarcamesine. Dizziness (35.8%



(a) ADAS-Cog13 results

Supplementary Table 1. Accumulated dose exposure to blarcamesine of 30 mg and 50 mg target groups by study visit, ITT population.

Treatment Group	Statistics	Week 12	Week 24	Week 36	Week 48
Blarcamesine 30 mg	n	154	123	116	113
	Mean (SD)	879·0 mg (392·02)	3032·6 mg (801·30)	5166·1 mg (1259·72)	7432·4 mg (1825·59)
Blarcamesine 50 mg	n	143	100	96	92
	Mean (SD)	825·1 mg (512·89)	3273·2 mg (1435·52)	5729·5 mg (2493·16)	8110·2 mg (3501·94)

Statistics of accumulated exposure to blarcamesine per study visit period in 30 mg/50 mg assigned target dosage groups in the ITT population at the time of each analysis visit.

(b) Accumulated blarcamesine dose

Figure 9. Results of the ADAS-Cog13 co-primary endpoint, split by dosage group Fig. 9a and the accumulated exposure table Fig. 9b [47].

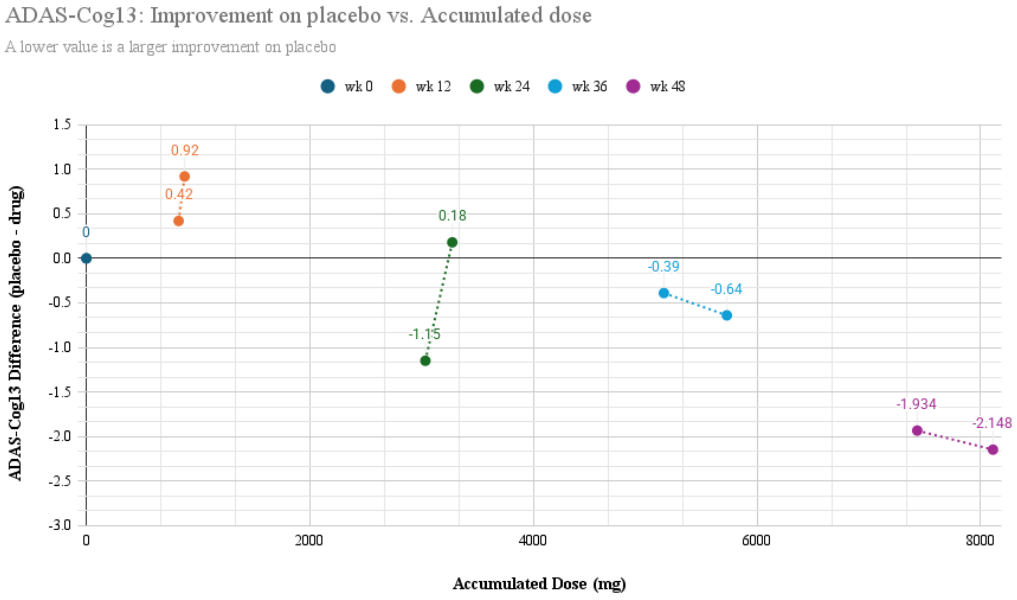


Figure 10. Improvement on placebo in the ADAS-Cog13 measurement is plotted against accumulated dose at each week. An inverse dose response appears for weeks 0-24 and a standard dose response for week 36 and 48. Adapted from data in Fig. 9.

Table 3
Adverse events summary, full safety population.

Adverse Events Summary	Blarcamesine 30 mg	Blarcamesine 50 mg	Blarcamesine	Placebo
Patients, n	167	168	335	168
Death, n (%)	0	1 (0.6)	1 (0.3)	1 (0.6)
Death considered related to treatment	0	0	0	0
Participants with ≥1 Serious TEAEs, n (%)	25 (15.0)	31 (18.5)	56 (16.7)	17 (10.1)
TEAE, n (%)	159 (95.2)	165 (98.2)	324 (96.7)	129 (76.8)
TEAE leading to Treatment and Study Discontinuation, n (%)	41 (24.6)	67 (39.9)	108 (32.2)	12 (7.1)
Blarcamesine Titration AE ≥5.0%, n (%)	167	168	335	168
Dizziness	53 (31.7)	67 (39.9)	120 (35.8)	10 (6.0)
Confusional state	24 (14.4)	24 (14.3)	48 (14.3)	1 (0.6)
Balance disorder	12 (7.2)	13 (7.7)	25 (7.5)	1 (0.6)
Fatigue	9 (5.4)	10 (6.0)	19 (5.7)	0 (0)
Anxiety	8 (4.8)	10 (6.0)	18 (5.4)	0 (0)
Nausea	8 (4.8)	13 (7.7)	21 (6.3)	8 (4.8)
Blarcamesine Maintenance AE ≥5.0%, n (%)	148	153	301	161
Dizziness	28 (18.9)	48 (31.4)	76 (25.2)	9 (5.6)
Confusional state	16 (10.8)	24 (15.7)	40 (13.3)	4 (2.5)
Fall	12 (8.1)	9 (5.9)	21 (7.0)	16 (9.9)
Depressed mood	8 (5.4)	7 (4.6)	15 (5.0)	3 (1.9)
Headache	8 (5.4)	11 (7.2)	19 (6.3)	6 (3.7)
Anxiety	6 (4.1)	11 (7.2)	17 (5.6)	6 (3.7)
Balance Disorder	5 (3.4)	11 (7.2)	16 (5.3)	2 (1.2)

Figure 11. Table from [2] showing the adverse events during the trial.

drug group vs 6% placebo), confusion (14.3% drug group vs 0.6% placebo) and balance disorder (7.5% drug group vs 0.6% placebo) show a clear pattern of adverse events that are especially problematic for a neurodegenerative disease patient population. In Alzheimer's patients, even"mild" dizziness or confusion can increase fall risk, loss of independence, and caregiver burden.

In addition to the adverse events, the drug group had a large rate of early terminations due to adverse events (see Fig. 12). In the 30mg group, 24.6% of patients terminated due to adverse events, and the rate was even worse in the 50mg group at 38.7% of patients. The adverse event-related drop out rate in the placebo cohort was just 7.7%. In the first 12 weeks, 57 patients dropped out from the drug groups compared to 17 for the placebo group. The explanation for this was that the aggressive titration of drug dosage in the first weeks induced AEs in the therapeutic group and that these could be avoided by altering the titration schedule in an approved dosing schedule. The study authors also claim that the early discontinuations did not introduce a bias in favor of blarcamesine. I disagree with this point. Alzheimer's is a disease that gradually accelerates in progression. In an effective drug, one would hope to see a slow down in degeneration vs placebo at a later time. If the weakest members of the drug group are forced to discontinue early due to AEs, then the drug group will clearly show less degeneration compared to the placebo group. It is therefore possible that the supposed improvement in the ADAS-Cog13 and the secondary endpoint CDR-SB is simply an artifact of the **drug population being filtered into a healthier population than the placebo group**.

4.5 Right Patient; Wrong Medicine - Subgroup Analyses of Blarcamesine

The last gasp hope of Anavex management is to cherry pick the blarcamesine data to show some outperforming subgroup - in other words, ditching large swaths of the patient population. Although precision medicine is a real and promising area of treatment for many diseases, the "right patient, right medicine" approach by companies like Astrazeneca has not yet been proven for blarcamesine in a stratified study. In order for EMA approval to be granted for a subgroup, such as patients with the SIGMAR1 wild-type gene, the EMA would likely require a further clinical trial with stratification of patients into a gene-carrying group and a control group.

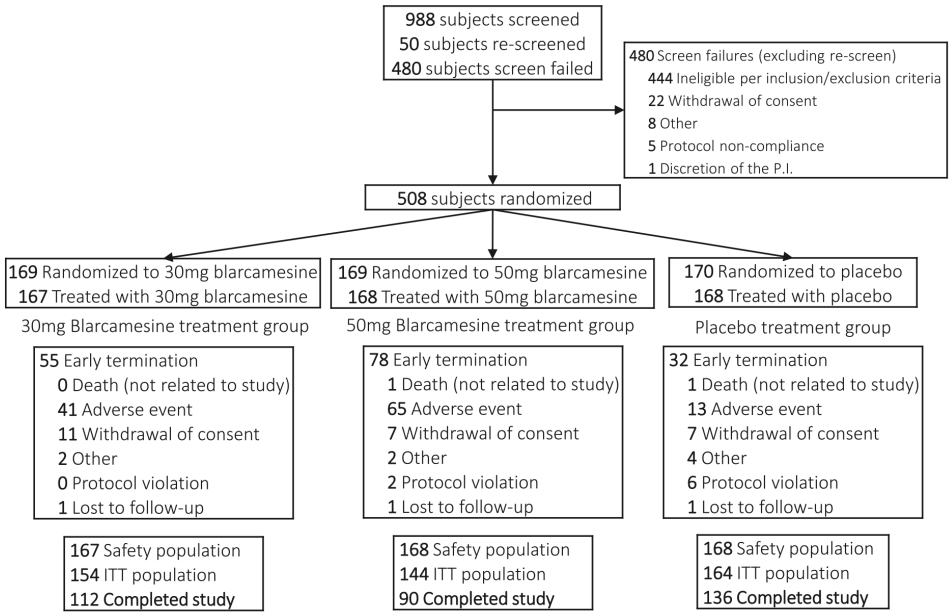


Fig. 1. Flowchart of patient screening, enrollment, discontinuation, and completion.

Figure 12. Patient enrollment flowchart from [2]

4.6 Drug Successes and Arguments for Approval

Blarcamesine is a novel treatment for AD with a differentiated mechanism of action from existing treatments and patients are able to self-administer at home as the drug is a once daily oral capsule. Most importantly to the regulators, the drug addresses an important unmet need in the patient population as it does not introduce amyloid-related imaging abnormalities (ARIA), as it targets upstream cellular pathways and homeostasis instead of being an amyloid-targeting drug.

These facts are unavoidable and represent a small, but very real, risk that that CHMP will make a surprise positive recommendation.

5 Trade Setup

On the totality of evidence, I believe there is a **very strong likelihood that the CHMP rejects blarcamesine** and that this likelihood is being underpriced by the market. This section will detail the trade setup to profit from a CHMP rejection.

5.1 Timing

Management has guided that they expect the EMA decision in Q1 2026 [13]. However, they are likely referring to the final EMA acceptance/rejection, and the stock will move based on the published CHMP recommendation.

Blarcamesine was submitted to the EMA for approval in November 2024. *Usually*, it takes around one year for the assessment [48].

The assessment of the application takes a maximum of 210 active days, i.e. days exclusive of stop-clocks. The first stage of evaluation lasts 120 days and the developer then gets up to three months to answer the CHMP's questions, during which time there is a stop clock until the answers are received. Anavex answered the first questions some time before the September meeting and restarted the clock, which hit 180 days at the September meeting. Anavex then received a LoOI and the stop-clock was again started.

According to the EMA, the developer usually has 1 month to respond [48]. This would then restart the clock and we would expect a decision to be given to Anavex within 30 days. That means we could see a decision occur at the October meeting, but that is unlikely as it would involve either one or both of the parties working incredibly quickly. More likely, the decision will come after the November or December meetings. Management will be informed of the decision directly and may decide to release a press release after receiving it. Since the meeting highlights are published online, we will be guaranteed to hear the decision via the CHMP if management withholds it. So, September (180 days) plus 30 remaining days takes us to October 18th. We add on however long it takes management to respond to the LoOI, say at least a month, and that takes us to November 18th. The November meeting ends on the 13th, so we can likely expect the results to come after the December meeting, on the 11th of December.

However, Anavex management have shown a past tendency to delay the inevitable in order to further milk ATM offerings. Therefore, we can not exclude the possibility that management pursues an oral explanation meeting with the CHMP which could cause significant delays. I personally view this as unlikely, but one must exercise caution.

CHMP meetings in 2023, 2024, 2025 and 2026

Month	2023	2024	2025	2026
January	23, 24, 25, 26	22, 23, 24, 25	27, 28, 29, 30	26, 27, 28, 29
February	20, 21, 22, 23	19, 20, 21, 22	24, 25, 26, 27	23, 24, 25, 26
March	27, 28, 29, 30	18, 19, 20, 21	24, 25, 26, 27	23, 24, 25, 26
April	24, 25, 26[2]	22, 23, 24, 25	22, 23, 24, 25	20, 21, 22, 23
May	22, 23, 24, 25	27, 28, 29, 30	19, 20, 21, 22	18, 19, 20, 21
June	19, 20, 21, 22	24, 25, 26, 27	16, 17, 18, 19	22, 23, 24, 25
July	17, 18, 19, 20	22, 23, 24, 25	21, 22, 23, 24	20, 21, 22, 23
August[1]	14, 15, 16, 17	19, 20, 21, 22	18, 19, 20, 21	17, 18, 19, 20
September	11, 12, 13, 14	16, 17, 18, 19	15, 16, 17, 18	14, 15, 16, 17
October	09, 10, 11, 12	14, 15, 16, 17	13, 14, 15, 16	12, 13, 14, 15
November	06, 07, 08, 09	11, 12, 13, 14	10, 11, 12, 13	09, 10, 11, 12
December	11, 12, 13, 14	09, 10, 11, 12	08, 09, 10, 11	07, 08, 09, 10

Figure 13. CHMP Meeting dates 2023 - 2026 [49]

Additionally, management may decide to withdraw their application if they deem its chances of getting approved to be zero. In doing this, management will buy themselves further time and will enable them to submit applications to other agencies without being tarnished by a negative CHMP opinion.

With Anavex's execution date likely to be before the end of the year, it is likely safe to buy Jan'26 puts.

5.2 Price Target

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	**AVXL share price**	**$8.90**											
2													
3	**Nov'25 Puts**				**Profit at target**								
4	**Strike**	**Premium**	**Breakeven**	**B/e change**	**$5.00**	**$4.50**	**$4.00**	**$3.50**	**$3.00**	**$2.75**	**$2.50**	**$2.25**	
5	**$4.00**	$0.15	$3.85	-56.74%	-100.00%	-100.00%	-100.00%	233.33%	566.67%	733.33%	900.00%	1066.67%	
6	**$5.00**	$0.20	$4.80	-46.07%	-100.00%	150.00%	400.00%	650.00%	900.00%	1025.00%	1150.00%	1275.00%	
7	**$6.00**	$0.30	$5.70	-35.96%	233.33%	400.00%	566.67%	733.33%	900.00%	983.33%	1066.67%	1150.00%	
8	**$7.00**	$0.60	$6.40	-28.09%	233.33%	316.67%	400.00%	483.33%	566.67%	608.33%	650.00%	691.67%	
9	**$8.00**	$1.00	$7.00	-21.35%	200.00%	250.00%	300.00%	350.00%	400.00%	425.00%	450.00%	475.00%	
10	**$9.00**	$1.58	$7.42	-16.63%	153.16%	184.81%	216.46%	248.10%	279.75%	295.57%	311.39%	327.22%	
11	**$10.00**	$2.23	$7.77	-12.70%	124.22%	146.64%	169.06%	191.48%	213.90%	225.11%	236.32%	247.53%	
12													
13	**Jan'26 Puts**				**Profit at target**								
14	**Strike**	**Premium**	**Breakeven**	**B/e change**	**$5.00**	**$4.50**	**$4.00**	**$3.50**	**$3.00**	**$2.75**	**$2.50**	**$2.25**	
15	**$4.00**	$0.43	$3.57	-59.89%	-100.00%	-100.00%	-100.00%	16.28%	132.56%	190.70%	248.84%	306.98%	
16	**$5.00**	$0.75	$4.25	-52.25%	-100.00%	-33.33%	33.33%	100.00%	166.67%	200.00%	233.33%	266.67%	
17	**$6.00**	$1.15	$4.85	-45.51%	-13.04%	30.43%	73.91%	117.39%	160.87%	182.61%	204.35%	226.09%	
18	**$7.00**	$1.65	$5.35	-39.89%	21.21%	51.52%	81.82%	112.12%	142.42%	157.58%	172.73%	187.88%	
19	**$8.00**	$2.20	$5.80	-34.83%	36.36%	59.09%	81.82%	104.55%	127.27%	138.64%	150.00%	161.36%	
20	**$9.00**	$2.80	$6.20	-30.34%	42.86%	60.71%	78.57%	96.43%	114.29%	123.21%	132.14%	141.07%	
21	**$10.00**	$3.40	$6.60	-25.84%	47.06%	61.76%	76.47%	91.18%	105.88%	113.24%	120.59%	127.94%	
22													
23	**Apr'26 Puts**				**Profit at target**								
24	**Strike**	**Premium**	**Breakeven**	**B/e change**	**$5.00**	**$4.50**	**$4.00**	**$3.50**	**$3.00**	**$2.75**	**$2.50**	**$2.25**	
25	**$4.00**	$0.80	$3.20	-64.04%	-100.00%	-100.00%	-100.00%	-37.50%	25.00%	56.25%	87.50%	118.75%	
26	**$5.00**	$1.12	$3.88	-56.40%	-100.00%	-55.36%	-10.71%	33.93%	78.57%	100.89%	123.21%	145.54%	
27	**$6.00**	$1.58	$4.42	-50.34%	-36.71%	-5.06%	26.58%	58.23%	89.87%	105.70%	121.52%	137.34%	
28	**$7.00**	$2.07	$4.93	-44.61%	-3.38%	20.77%	44.93%	69.08%	93.24%	105.31%	117.39%	129.47%	
29	**$8.00**	$2.70	$5.30	-40.45%	11.11%	29.63%	48.15%	66.67%	85.19%	94.44%	103.70%	112.96%	
30	**$9.00**	$3.40	$5.60	-37.08%	17.65%	32.35%	47.06%	61.76%	76.47%	83.82%	91.18%	98.53%	
31	**$10.00**	$4.20	$5.80	-34.83%	19.05%	30.95%	42.86%	54.76%	66.67%	72.62%	78.57%	84.52%	
32													

(a)

	A	C	D	E	F	G	H	I	J	K	L	M	N
1	Quarter	Q2 2023	Q3 2023	Q4 2023	Q1 2024	Q2 2024	Q3 2024	Q4 2024	Q1 2025	Q2 2025	Q3 2025	Q4 2025	Q1 2026
2	Date	31/03/2023	30/06/2023	30/09/2023	31/12/2023	31/03/2024	30/06/2024	30/09/2024	31/12/2024	31/03/2025	30/06/2025	30/09/2025	31/12/2025
3	Cash	153466962	154817164	151024000	143765000	139386000	138756000	132187000	120775000	115771000	101164000	94164000	87164000
4	Cash After 150MM	153466962	154817164	151024000	143765000	139386000	138756000	132187000	120775000	115771000	101164000	244164000	237164000
5	Shares Out	78304363	80875235	81973250	82077815	82464226	84535328	84795517	84805974	85073769	85085795	85085795	85085795
6	**Shares Out after 150MM**											**100,085,795**	**100,085,795**
7	**Cash/Share**	**$1.96**	**$1.91**	**$1.84**	**$1.75**	**$1.69**	**$1.64**	**$1.56**	**$1.42**	**$1.36**	**$1.19**	**$1.11**	**$1.02**
8	**Cash/Share after 150MM**											**$2.44**	**$2.37**

(b)

Figure 14. 14a $AVXL Put options payoff matrix for various strikes and expiration dates, premium is last or mid-price for the option and 14b cash on hand of Anavex Life Sciences. If the ATM is fully utilised, expect cash to be $2.37 per share by Q1'26, otherwise $1.02.

The price target of $AVXL is hard to predict. Anavex has been steadily burning cash and printing shares, driving cash per share lower. In fig. 14b I assume that over Q4 2025 and Q1 2026 Anavex burns a conservative $7MM per quarter and may fully dilute using the $150MM ATM offering (as discussed in Sec. 2.1.1). That means we end 2025 with $1 per share in cash in the case where management doesn't use the ATM (unlikely) and with $2.37 where they fully use the ATM. Should $AVXL trade down to these levels on CHMP rejection? Yes. Will it? I doubt it.

Management will do whatever they can to obfuscate the future outlook of blarcamesine, despite CHMP likely destroying future prospects. Additionally, the recent phase II schizophrenia trial results were able to pump the stock above $10 in early October 2025. However, management may likely try to further spin results of this trial, dredging whatever cherry-picked subgroup they can find to show some efficacy. This *may* muddy the waters and cause a stock price to remain stubbornly above cash. This may make the anticipated share price move be more muted than expected.

With this, I would expect $AVXL to trade at least $1-2\times$ cash post-CHMP opinion. This would give a price target of $2.37-$4.74 per share (assuming $150MM ATM use, otherwise: $1.02-$2.04), a potential 76% drop from it's closing price on the 3rd of October 2025.

5.3 Options Play

I've put together an options payoff matrix in fig. 14a. The likely chance that the CHMP opinion comes after the November options expiration date and the lack of liquidity of the April expiry options makes the January puts the only appealing play. Taking my price target, any strike above $6 looks attractive. Baking

in a larger margin for error (for retail pumps, ATM dilution etc.), I would personally want to be in profit with the stock price at anywhere sub-$5. For that reason, I would be looking at purchasing a ladder of $6/7/8/9 January 2026 puts, all of which would return well over 100% if the lower bound of the price target is met.

6 Disclosure

No part of this document should be considered as investment advice. Any stock trade is inherently risky. Shorting stocks is even more so, as you stand to make unlimited losses by shorting stocks. Purchasing options contracts could result in you losing all your premium. Do not trade based on the information in this report. This report is not a solicitation to buy or sell any security. Do your own due diligence. This Report is solely for educational purposes and constitutes impersonal, generic commentary based entirely on publicly available data from public sources only. The views expressed herein reflect the personal opinions of the author as of the date of publication and are subject to change without notice; they are not tailored to any individual's financial situation or objectives and do not constitute investment advice, a recommendation, or an offer to buy or sell any security. The author holds a short position in the securities discussed, which may change at any time without notice. No part of the author's compensation is, was, or will be directly or indirectly related to any specific recommendation or view contained herein. The author has not received—and will not receive—any payment of any kind from the company(ies) whose securities are covered by this Report. This Report contains no material non-public information. All factual data are believed to be accurate at the time of writing, but the author makes no warranty as to its completeness or accuracy, and there may be errors or omissions; recipients should conduct their own due diligence. This Report does not rely on anonymous sources. Past performance is not indicative of future results.

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