Blarcamesine Data Bloated with BS (Bad Statistics): A Short Sell Report on Anavex (NASDAQ: AVXL)

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I. Executive Summary

This report details the assessment of Anavex Life Sciences (NASDAQ: AVXL) and its EMA Marketing Authorisation Application (MAA) for Blarcamesine (ANAVEX2-73), an oral sigma-1 receptor agonist, for the treatment of early Alzheimer's disease. The application is supported by two studies: a small, proof-of-concept Phase 2a trial (NCT02244541) and the larger, pivotal Phase 2b/3 trial ANAVEX2-73-AD-004 (NCT03790709). Because the Phase 2a study is underpowered, our analysis focuses on the Phase 2b/3 data.

The assessment concludes that the publicly available data is insufficient to support a marketing authorisation. It is marked by several fundamental deficiencies that preclude a positive benefit-risk determination. The pivotal trial failed to meet one of its two co-primary endpoints, the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL), a critical measure of function. The statistically significant result observed on the other co-primary endpoint, the Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog13), is judged to be statistically fragile and of questionable clinical relevance. Its robustness is severely undermined by methodological issues, including an implausibly applied statistical model for missing data, a lack of dose-response, and a delayed onset of effect.

Furthermore, the application lacks confirmatory evidence from key biomarkers of neurodegeneration. There was no significant effect on plasma p-Tau or Neurofilament Light chain (Nf-L), markers considered essential for substantiating a disease-modifying claim. The safety profile, while favourably distinguished by an absence of Amyloid-Related Imaging Abnormalities (ARIA), is compromised by exceptionally poor tolerability. High rates of dizziness and confusional states led to an unacceptably high and differential dropout rate (32.2% in the treatment group vs. 7.1% in the placebo group), which introduces significant bias and compromises the integrity of the trial data.

Compounding these issues are serious concerns regarding transparency and data reporting. The sponsor has failed to provide a publicly available Statistical Analysis Plan (SAP), and there have been unexplained, material improvements in reported p-values between initial press releases and the final publication, alongside selective reporting of outcomes. These practices fall short of the rigorous standards expected for an MAA submission. Alarmingly, these actions mirror past accusations against Anavex concerning its Rett syndrome trial data. For investors, this suggests a potential pattern of behaviour that severely damages credibility with regulators and the market, jeopardising the submission's integrity and future trust in the company's announcements.

In light of the totality of evidence, the benefit-risk balance for Blarcamesine is deemed negative. The modest and unreliable evidence of benefit does not outweigh the risks associated with poor tolerability and the profound uncertainties regarding the validity of the data. A second, robust, and prospectively designed confirmatory trial would be required to reconsider this product.

Final Recommendation Probabilities

Full Approval: 0%

Justification (Robustness, Data Integrity, Precedent): The application fails to meet the fundamental regulatory requirement for robust and consistent evidence from adequate and well-controlled studies. A single trial with a failed co-primary endpoint, a statistically fragile positive co-primary, inconsistent reporting, and weak biomarker support does not provide the totality of evidence necessary for full authorisation under Article 8(3) of Directive 2001/83/EC.

Conditional Approval (under exceptional circumstances): <1%

Justification (Benefit-Risk, Unmet Need, Confirmatory Data): While a high unmet medical need exists, conditional marketing authorisation requires that the benefit-risk balance is positive, albeit with less comprehensive data. The questionable validity of the efficacy signal, driven by profound methodological issues (e.g., high informative dropout, model dependency), and the lack of a confirmed biological effect on core neurodegeneration markers make it difficult to conclude that the benefits of Blarcamesine outweigh its risks. EMA precedent, including the recent negative opinion on donanemab in March 2025, underscores the agency's consistently high evidentiary threshold for demonstrating a positive benefit–risk balance, even when a commitment to provide post-authorisation data exists. Furthermore, the EMA has repeatedly emphasised that exploratory subgroup analyses alone are insufficient for approval, viewing such findings as hypothesis-generating unless supported by prospectively validated evidence.

Taken together, the current data package does not provide adequate assurance of a clinically meaningful benefit to warrant conditional approval, even under exceptional circumstances

CHMP Opinion Readout and Price Impact:

As of this report dated July 13, 2025, Anavex Life Sciences (NASDAQ: AVXL) is trading at US $11.11 per share. A negative CHMP opinion is the most likely outcome, expected shortly after the September 18 or October 16 2025 meeting, likely triggering an immediate price drop exceeding 70%, driven by elevated short interest (~33% of float). Near-term price stabilisation is anticipated around or below US $2.80 per share, reflecting modest residual value assigned to the broader pipeline

II. Assessment of Clinical Efficacy

A. Analysis of Co-Primary and Secondary Endpoints: A Statistically Divided Outcome

The ANAVEX2-73-AD-004 trial was designed as a Phase 2b/3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of Blarcamesine in patients with early Alzheimer's disease. The study protocol pre-specified two co-primary endpoints to be assessed at 48 weeks: the 13-item Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog13) to measure cognition, and the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) scale to measure function.

According to the final publication by Macfarlane et al. (2025), the trial yielded a statistically divided result on these co-primary endpoints. For ADAS-Cog13, the combined Blarcamesine group showed a least-squares mean (LSM) difference versus placebo of -2.027 (95% CI [-3.522 to -0.533]), with a corresponding p-value of $p=0.008$. In contrast, the ADCS-ADL endpoint failed to demonstrate a statistically significant difference, with an LSM difference of 0.775 (95% CI [-0.874 to 2.423]) and a p-value of $p=0.357$.

The sponsor asserts in the publication abstract that "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 $P<0.025$". This statement is a misleading re-framing of the trial's outcome. The Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) was a pre-specified secondary endpoint, not a co-primary one. The attempt to substitute a successful secondary endpoint for a failed co-primary endpoint post-hoc is not an acceptable practice for interpreting the primary success of a trial. From a regulatory standpoint, this outcome represents a fundamental failure.

Furthermore, the sponsor separately argues that achieving significance on the single ADAS-Cog endpoint should be considered a *"win"*, citing purported FDA guidance that a sole cognitive endpoint is sufficient for early Alzheimer's disease studies. This justification is also flawed. Not only does this argument use

promotional rather than precise regulatory language, but it also critically ignores the fact that the company is dealing with the more conservative EMA, not the FDA, making the appeal to a different agency's potential flexibility irrelevant. The EMA's scientific guideline on the clinical investigation of medicines for Alzheimer's disease (CPMP/EWP/553/95 Rev. 2) explicitly states that for mild to moderate AD, it is necessary to demonstrate an effect on both cognition and functioning to ensure the clinical meaningfulness of the treatment effect, for which a co-primary endpoint approach is required. The clear failure of the ADCS-ADL endpoint ($p=0.357$) means the trial did not meet its pre-specified primary objective as defined by established regulatory standards. The argument that the secondary endpoint CDR-SB showed a statistically significant result (LSM difference -0.483, $p=0.010$) does not rectify the failure of the functional co-primary endpoint. While the CDR-SB is a valuable composite measure, in most cases, it cannot retroactively replace a failed primary endpoint in the hierarchical testing structure of a confirmatory trial. Therefore, the trial should be considered as having only partially met its objectives, a status that is insufficient for a claim of robust efficacy.

B. Temporal Profile and Dose-Response: Lack of Pharmacological Consistency

A detailed examination of the efficacy data reveals further weaknesses that undermine the biological plausibility of the observed treatment effect. First, the profile of efficacy is atypical and inconsistent with established disease-modifying or symptomatic treatments for Alzheimer's disease, as well as nearly all medicines. Second, data collection lasted only 48 weeks, which is relatively short for an Alzheimer's disease trial. Given the delayed separation between groups and the absence of early efficacy, a longer study duration would have been essential to establish a durable and clinically meaningful treatment effect.

The efficacy curves for both ADAS-Cog13, ADCS-ADL and CDR-SB, as analysed by a Mixed Model for Repeated Measures (MMRM), the Blarcamesine group performed numerically worse than placebo for the first 12 weeks of the study, and even at 24 weeks (**Figure 1**). The statistically significant separation from placebo only emerged at the final 48-week timepoint. This delayed effect contrasts sharply with the early and sustained separation from placebo typically observed with approved agents like the acetylcholinesterase inhibitors donepezil and galantamine **(appendix Figure 1A)**, as well as the anti-amyloid antibody lecanemab, whose effects are all evident within the first few weeks and months of treatment.

The sponsor's explanation that the poor early performance was due to initial tolerability issues is not convincing, as an analysis of completers who remained in the trial until Week 48 (i.e., excluding post–Week 12 dropouts) still underperformed placebo at the Week 12 timepoint (**Appendix Figure 2A**), suggesting a genuine lack of early drug effect rather than a transient tolerability artifact. They use this underperformance as a pretext to claim that *"there is no evidence that early termination will introduce a bias in favor of blarcamesine."* We will explain in Section IV why dropout would still have probably biased the data in favour of blarcamesine.

While the sponsor attributes the early underperformance to the steep up-titration during the first few weeks, this lacks credibility. The titration period was limited to the first 2 to 3 weeks, yet blarcamesine patients continued to underperform placebo through Week 12, even among study completers. Moreover, if the delayed efficacy signal were instead due to longer-term persisting side effects, such as dizziness or confusional states, both of which were common and sustained, this would reflect a more serious concern, not a mitigating factor. In either case, the failure to demonstrate early benefit undermines the biological plausibility of the treatment effect and raises questions about both tolerability and pharmacological activity.

Figure 1. Clinical efficacy endpoints

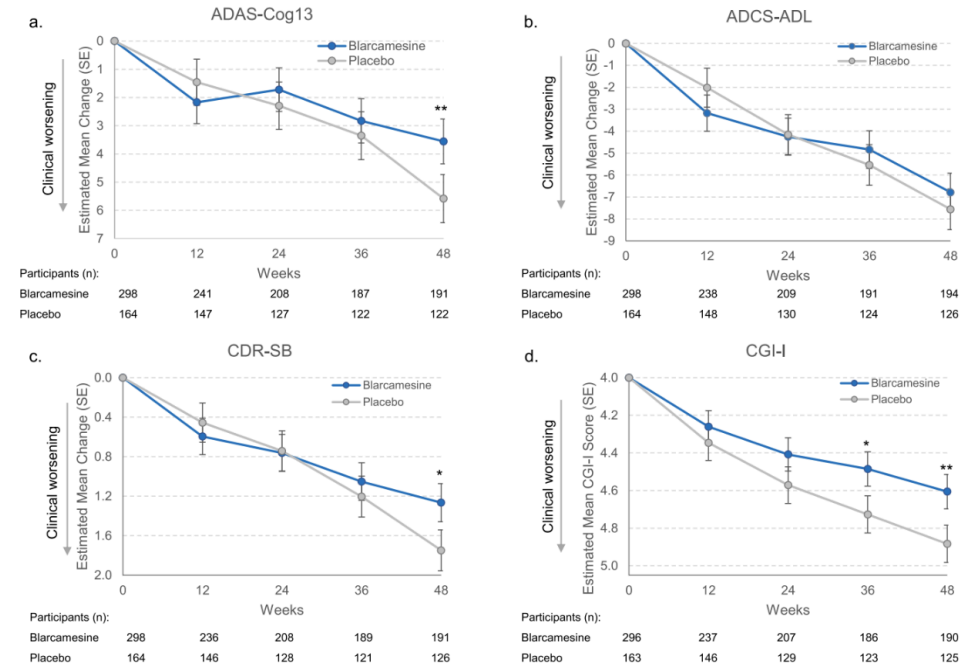


Fig. 2. Clinical efficacy endpoints estimated mean change from baseline, blarcamesine versus placebo, ITT population.
Clinical efficacy endpoints were analyzed using mixed model for repeated measures (MMRM) estimates for the least-squares mean change from baseline at 12, 24, 36, and 48 weeks, with error 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,**: $p < 0.01$.

Secondly, the trial fails to show a clear dose-response relationship, as the overlaid supplementary 30 mg and 50 mg dose groups had nearly identical efficacy curves (Figure 2). At several points, the 30 mg dose performed better, showing a more significant p-value on the CDR-SB scale (p=0.020) compared to the higher 50 mg dose (p=0.045). This lack of a dose-dependent effect is likely explained by the study's flexible dosing design, which is likely pre-specified. The protocol allowed for dose reductions (to a minimum of 10mg/day in the maintenance phase) for any reason, which resulted in the two active treatment groups receiving similar cumulative drug exposure throughout the study, making it difficult to discern a true dose-response.

The absence of these two key hallmarks of a robust drug effect, early onset and a clear dose-response, casts significant doubt on the validity of the single positive result at Week 48. It suggests that the observed effect may not be a genuine pharmacological one, but rather a statistical artifact arising from other trial dynamics, such as the high and differential dropout rates. EMA guidelines explicitly favour trial designs that can demonstrate dose dependency, and its absence here weakens the overall case for efficacy.

Figure 2. ADAS-Cog13 and CDR-SB Outcomes Reveal Similar or Inconsistent Efficacy Between overlaid Blarcamesine 30 mg and 50 mg Arms Over Time

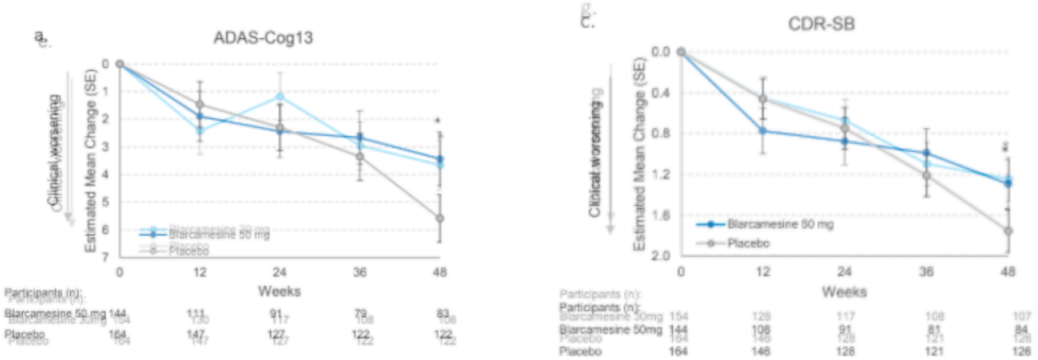


Table 1. The 50 mg arm accumulates more exposure than the 30 mg arm, but not as much as expected based on the nominal dose.

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.

C. Pharmacogenomic Subgroup Analysis (SIGMAR1): Exploratory, Not Confirmatory

The MAA submission places considerable emphasis on a pre-specified pharmacogenomic subgroup analysis based on a variant in the Sigma-1 receptor gene (SIGMAR1, rs1800866).

The analysis reported that participants with the common wild-type (WT) SIGMAR1 genotype (~70–80% of the study population) experienced a numerically greater and statistically significant treatment effect. In this subgroup, the least squares mean (LSM) difference between blarcamesine and placebo was −2.317 on ADAS-Cog13 (95% CI: −4.182 to −0.453; 49.8% less decline; P = 0.015) and −0.601 on CDR-SB (95% CI: −1.070 to −0.133; 33.7% less decline; P = 0.012) **- see appendix Table 2A**. In contrast, among rs1800866 variant carriers (n = 87/58 blarcamesine/placebo), the ADAS-Cog13 difference was −1.593 (95% CI: −4.174 to +0.989; 25.2% less decline; P = 0.225), and for CDR-SB it was −0.230 (95% CI: −0.826 to +0.367; 13.6% less decline; P = 0.449), neither reaching significance.

Interestingly, the lower bounds of the confidence intervals for ADAS-Cog13 were nearly identical in both subgroups (~−4.18), yet the WT subgroup's upper bound was only −0.453, just above zero, while the carrier subgroup extended to +0.989. If the WT group were truly more responsive, a substantially more favourable upper bound would be expected, reflecting a stronger response. The modest shift suggests the observed difference may not reflect a robust biological effect. Moreover, no formal test of genotype-by-treatment interaction was reported, limiting confidence in the claim that SIGMAR1 genotype meaningfully modifies treatment response.

While these findings are hypothesis-generating, they must be considered strictly exploratory and carry no confirmatory weight for regulatory approval. The analysis suffers from several critical methodological deficiencies that are unacceptable for a pivotal claim. Randomisation was not stratified by SIGMAR1 genotype. This introduces a high risk of baseline imbalances between the treatment and placebo arms within the subgroup, which could confound the results. The analysis was not part of the primary, multiplicity-controlled testing hierarchy. The reported p-values are nominal and have not been adjusted for the multiple endpoints and subgroups tested, inflating the risk of a Type I error (a false positive finding). Further, the sponsor failed to report a formal treatment-by-genotype interaction p-value. This statistical test is essential to determine whether the drug's effect is statistically different between the WT and variant carrier groups. Without it, one can only state that the drug appeared to work in one group and not the other, not that the genotype is a true predictor of differential response. Finally, the results for the co-primary functional endpoint, ADCS-ADL, were not reported for the SIGMAR1 subgroup. This selective omission prevents a comprehensive assessment of the drug's effect on both cognition and function within this population of interest.

For a subgroup analysis to be considered confirmatory by the EMA, it must be based on a prospectively defined, adequately powered, and stratified population, with appropriate adjustments for multiplicity and

formal interaction testing. The SIGMAR1 analysis meets none of these criteria. It stands in stark contrast to the rigorous, stratified subgroup analyses based on APOE4 status and tau burden that supported the regulatory submissions for lecanemab and donanemab.

The following table summarises the regulatory deficiencies of the Blarcamesine SIGMAR1 subgroup analysis compared to established confirmatory standards.

Table 2: Regulatory deficiencies of the Blarcamesine SIGMAR1 subgroup analysis compared to established confirmatory standards with lecanemab and donanemab

Factor	Blarcamesine (SIGMAR1)	Confirmatory Standard (e.g., Lecanemab/Donanemab)	Regulatory Implication
Stratified Randomization	No	Yes	High risk of baseline confounding and bias.
Multiplicity Adjustment	No (Nominal p-values)	Yes (Part of hierarchical testing)	Inflated risk of false-positive findings; cannot be considered confirmatory.
Interaction Testing	Not Reported	Yes for (Formal interaction p-values reported)	Inability to conclude a statistically significant differential treatment effect.
Complete Endpoint Reporting	No (ADCS-ADL missing)	Yes (All primary/key secondary endpoints reported)	Prevents assessment of consistency across cognitive and functional domains.
Regulatory Weight	Exploratory / Hypothesis-Generating	Confirmatory	Cannot be used as a basis for marketing authorisation.

In summary, the SIGMAR1 subgroup results, while intriguing, do not meet the evidentiary threshold for regulatory decision-making and would require validation in a new, prospectively designed and adequately powered trial.

III. Evaluation of the Safety and Tolerability Profile

A. Benefit-Risk Analysis: An ARIA-Free Profile Undermined by Poor Tolerability

While Anavex highlights a significant safety advantage for blarcamesine due to the absence of amyloid-related imaging abnormalities (ARIA) in its ANAVEX2-73-AD-004 study, a key point of differentiation from anti-amyloid monoclonal antibodies that require intensive MRI monitoring, this claim is complicated by other aspects of the data. The sponsor also reported high study drug compliance, with a mean of 96% in the combined blarcamesine group and 99% in the placebo group, based on actual days of exposure relative to planned exposure.

However, this apparent safety benefit is profoundly undermined by the drug's questionable tolerability profile. The sponsor touts the absence of ARIA as a key advantage, yet paradoxically suggests in the conclusion that the drug could also be used alongside anti-amyloid therapies that cause ARIA. This contradictory positioning undermines both its claimed safety edge and any argument for stand-alone efficacy, further weakening the overall benefit–risk case.

Contrary to the narrative of tolerability, the trial data show a high incidence of adverse events. In the combined blarcamesine group, 96.7% of patients experienced at least one treatment-emergent adverse event (TEAE), compared to 76.8% in the placebo group (see Table 3). Neurological adverse events were particularly burdensome, with dizziness reported in 35.8% of blarcamesine patients versus 6.0% in the placebo group, and confusional state reported in 14.3% versus 0.6% during the titration phase. These effects persisted at high rates into the maintenance phase. This directly led to an unacceptably high and differential discontinuation rate of 32.2% due to adverse events in the blarcamesine group, compared to only 7.1% in the placebo group. This figure rose to 39.9% in the 50 mg arm.

Table 3: Adverse Event Summary

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)

The high rate of dropouts driven by adverse events (AEs) can introduce significant methodological challenges. Efficacy results may be influenced by a "survivor bias", where the data comes from a select group of patients who were able to tolerate the drug. This group may not accurately represent the broader Alzheimer's population, which includes individuals who might be sicker or less likely to respond. Furthermore, a high frequency of distinct side effects, such as neurological AEs, increases the likelihood of "functional unblinding." In this scenario, it may become apparent to both patients and investigators who is receiving the active drug versus the placebo. This can lead to "expectancy bias," particularly affecting subjective,

rater-based endpoints like the ADAS-Cog and CDR-SB, where an unblinded rater might unconsciously score a patient more favourably.

The high rate of dropouts driven by adverse events introduces significant methodological challenges. Efficacy results may be influenced by "survivor bias," where the data reflect only those patients who were able to tolerate the drug. This subgroup may not accurately represent the broader Alzheimer's population, which includes individuals who may be more frail or less responsive. Furthermore, the high frequency of distinct side effects, particularly neurological events, increases the likelihood of "functional unblinding." In this scenario, it may become apparent to both patients and investigators who is receiving the active drug versus placebo, which can lead to "expectancy bias" in subjective, rater-based endpoints such as ADAS-Cog and CDR-SB.

While it has been suggested that these tolerability issues could be addressed by adjusting to a slower titration, a lower target dose, and nighttime administration, there is no definitive way of knowing if these changes would be effective without conducting another formal clinical trial. In conclusion, although the absence of ARIA is a notable positive feature, it fails to compensate for the severe tolerability issues and the profound methodological compromises they introduce, which call into question the validity of the efficacy data itself and weaken the overall benefit-risk assessment.

IV. Scrutiny of Statistical Methodology and Data Integrity

A. The Missing At Random (MAR) Assumption and MMRM Analysis: A Flawed Foundation

The trial analysed its longitudinal efficacy endpoints with a Mixed Model for Repeated Measures (MMRM). MMRM is valid only if any missing data are Missing At Random (MAR), meaning the chance a data point is missing depends exclusively on information already observed (e.g., baseline characteristics or earlier test scores) and not on the unrecorded outcome the patient would have had. For example, a withdrawal because a participant relocates satisfies MAR, whereas a withdrawal driven by a sudden clinical decline that we never capture does not. If the latter occurs, the model preferentially retains patients who tolerate and benefit from treatment, inflating the apparent effect size.

In the context of the Blarcamesine trial, this assumption is highly implausible and likely violated. The data clearly show that dropout was not a random event. In the Blarcamesine group, a staggering 32.2% of patients discontinued, with the vast majority of these discontinuations attributed to TEAEs. In the crucial early phase of the trial (before Week 12), 90% of the 40 dropouts in the treatment arm were due to TEAEs (**appendix Table 4A and Figure 2A**). It is clinically logical and highly probable that patients who drop out due to adverse events like dizziness, falls, and confusional state are not tolerating the drug and are on a worse clinical trajectory than those who can tolerate it and remain in the study. This scenario, where the reason for dropout is directly related to the unobserved outcome (i.e., worsening condition), is the textbook definition of a Missing Not At Random (MNAR) data pattern.

Applying an MMRM model based on the MAR assumption to data that is likely MNAR introduces a systematic and significant risk of bias. The model effectively handles the missing data for the high number of dropouts by imputing values based on the trajectory of the "survivors"—the healthier, more tolerant patients who remained in the trial. This creates an overly optimistic estimation of the treatment effect at Week 48, as the negative outcomes of the intolerant dropouts are not properly accounted for. The final efficacy result is therefore highly model-dependent and likely an overestimation of the true drug effect.

A major transparency failure that compounds this issue is the sponsor's decision not to report a simple completer-only analysis for the 48-week endpoints. Presenting the observed data from only the patients who completed the study is a fundamental sensitivity analysis that would allow regulators to compare the raw, observed effect with the model-derived effect. The absence of this basic comparison prevents a full assessment

of the MMRM model's influence on the final result and deepens the concern that the headline efficacy claim is an artifact of the statistical modelling rather than a robust clinical finding.

B. Statistical Fragility and Tipping Point Analysis: An Effect on the Edge

Given the high rate of informative dropout, sensitivity analyses are critical to assess the robustness of the primary efficacy finding. The sponsor conducted a tipping point analysis to determine how much the outcomes for the dropout population would need to change to "tip" the primary result from statistically significant to non-significant. However, the sponsor's interpretation of this analysis is flawed and contrary to their claim, demonstrating the fragility, not the robustness, of their result.

The analysis showed that the ADAS-Cog13 result would lose statistical significance (at a $p < 0.05$ threshold) if the imputed values for dropouts in the active arm were assumed to be 1.90 points worse than the completers. This corresponds to an allowable erosion of the treatment effect (vs placebo) of just 0.425 points (from -1.973 to -1.548) before significance is lost (**Table 4)**. This exercise alters only the missing data for non-completers and does not capture the random sampling variation that would occur among completers if the trial were repeated, underscoring why regulators usually require confirmation in a second study.

Table 4. Sensitivity Analysis - Tipping Point Analysis

	ADAS-Cog13			
	Active Worsening		Placebo Improving	
MAR	Placebo	Active	Placebo	Active
LS Mean (SE)	5.664 (0.877)	3.691 (0.805)	5.664 (0.877)	3.691 (0.805)
LS Mean Diff (SE)		-1.973 (0.788)		-1.973 (0.788)
p-value		0.0124		0.0124
Tipping Point 1				
Shift		1.88	-3.20	
Shifted Mean	5.800	4.247	5.158	3.604
Shifted Diff		-1.553		-1.554
p-value		0.0499		0.0494
Tipping Point 2				
Shift		1.90	-3.30	
Shifted Mean	5.802	4.253	5.143	3.601
Shifted Diff		-1.548		-1.541
p-value		0.0506		0.0514

Results of the tipping point analysis compare the primary MMRM result, which uses the missing at random (MAR) assumption for all missing data, to an imputation model where data are missing not at random (MNAR), to find the point at which worsening of the active group or improvement of the placebo group would make the result non-significant ($p > 0.05$).

The sponsor argues this shows robustness because the observed treatment difference at 48 weeks was -1.973 points. This interpretation is incorrect. A tipping point analysis demonstrates robustness when the required shift to overturn the conclusion is so extreme as to be considered clinically implausible. Here, an assumed worsening of 1.90 points for dropouts (vs the completers) is not only plausible but results in a shifted mean for the active group (4.253) that is still a better outcome than the overall decline observed in the placebo group from the primary analysis (5.664), making it a very realistic scenario

The sponsor's tipping-point analysis used a significance threshold of $p < 0.05$. However, European Medicines Agency (EMA) guidelines for a study with two co-primary endpoints require a stricter, multiplicity-adjusted threshold of $p < 0.025$ for each. When the analysis is re-run using the correct EMA threshold, the fragility of the ADAS-Cog13 result becomes even more apparent. A slight negative change in the assumed outcomes for patients who dropped out of the study is sufficient to push the p-value above the 0.025 mark, thereby losing statistical significance. This demonstrates that even minor, justifiable shifts in the assumptions for missing

data can flip the borderline "positive" finding to non-significant under the required regulatory standard, as seen below in **Table 5**.

Table 5. Tipping Point Sensitivity Analysis Under EMA Standards — Minimum Assumed Worsening Required to Invalidate ADAS-Cog13 Significance ($p < 0.025$ Threshold)

Parameter	Value	Source / Calculation
Original Treatment Effect (LSM Diff) via MAR	-1.973 points	Supplemental Table 7
Standard Error (SE) of the Difference	0.788	Supplemental Table 7
Critical t-value for $p < 0.025$ (df ≈ 250-400)	~2.00	Welch's t-distribution table (approximation to account for the unequal sample sizes)
Minimum Effect for Significance at $p < 0.025$	-1.576 points	2.00×0.788
Allowable Erosion (Shifted Dif) of Treatment Effect	0.397 points	$-1.973-(-1.576)$
Required ADAS-Cog Worsening for Dropouts (assuming linear	~1.78-point Shift	(1.90-point Shift / 0.425-point Erosion) * 0.397-point Target Erosion ≈ 1.78-point Shift
Required Shift per Dropout Group (Balanced MNAR)	0.1985 points	Assumes equal shift: Blarcamesine dropouts worsen by 0.1985, Placebo dropouts improve by 0.1985. Total erosion = 0.397.
Shift as a Fraction of Standard Error	~0.50 SE	$0.397 \div 0.788$

This analysis argues that the positive result for the study's cognitive endpoint (ADAS-Cog13) is statistically fragile and likely insufficient to support a Marketing Authorisation Application (MAA) when evaluated

against appropriate regulatory standards. The reported treatment effect is only 0.397 points away from erasing statistical significance, a margin so small that an assumed shift of just 0.1985 points, worsening every blarcamesine dropout by +0.1985 and improving every placebo dropout by –0.1985 relative to their completers. Losing a result with a shift equivalent to only half a standard error is a clear indicator of an unreliable conclusion. While this analysis uses a simplified linear estimation, it is a valid local approximation that frames the conceptual risk. The true statistical relationship is more complex, governed by the MMRM model and Rubin's Rules for multiple imputation, and a full replication would require patient-level data. However, the conclusion of fragility is very likely to hold, as this simplified model effectively demonstrates the result's extreme sensitivity to small and plausible shifts in the missing data assumptions.

C. Potential P-Hacking: How Dose Pooling and Subgroup Framing Skewed Outcomes

The most likely scenario is that the decision to pool the 30 mg and 50 mg blarcamesine arms was made post hoc, driven by the need to strengthen borderline statistical results. In the initial analysis, each dose arm showed only modest and fragile statistical significance (e.g., ADAS-Cog13: $p = 0.026$ for 30 mg, $p = 0.021$ for 50 mg) (**appendix Table 3A)**. These marginal p-values, while technically significant, often fall short of the evidentiary threshold required for regulatory approval, especially when no correction for multiplicity is applied and other endpoints, such as ADCS-ADL, are non-significant. Faced with this, the sponsor appears to have "rescued" the result by pooling the two arms, knowing this would boost statistical power and reduce variance. As expected, the p-value improved substantially ($p = 0.008$), and the upper bound of the confidence interval became more favourable (−0.533, compared to −0.228 and −0.319 for 30 mg and 50 mg, respectively). To justify this manoeuvre, the sponsor invoked dose accumulation data suggesting similar drug exposure between the two arms, offering a convenient and superficially credible rationale.

However, the timing and nature of this adjustment suggest it was not part of a pre-specified analytic strategy, but rather a strategically motivated decision designed to enhance the appearance of efficacy. While not outright data fabrication, this represents a sophisticated form of p-hacking, where modelling choices are framed as scientifically justified but are primarily driven by the need to produce a positive result.

A parallel pattern appears in the SIGMAR1 rs1800866 wild-type subgroup (**appendix Table 2A)**. Although the subgroup was reportedly pre-specified, it remains unclear whether the decision to pool the 30 mg and 50 mg dose arms within this subgroup was also pre-defined. The individual dose results were again borderline: −2.302 (nominal $p = 0.031$) for 30 mg and −2.357 (nominal $p = 0.045$) for 50 mg, with upper bounds of −0.206 and −0.058. Pooling produced no real change in effect size (−2.317), but the p-value improved (nominal $p = 0.015$) and the upper bound became more favourable (−0.453), creating a stronger statistical impression. This mirrors the pattern observed in the ITT population, where pooling similarly enhanced statistical significance without improving the underlying effect size. Importantly, while the SIGMAR1 subgroup was pre-specified, it was not part of the primary hierarchical testing strategy and was not subject to multiplicity control. As a result, the p-values remain nominal and would not withstand standard correction for multiple comparisons (e.g., Bonferroni adjustment). No formal genotype-by-treatment interaction test was reported, and the absence of a dose-response further weakens the biological plausibility of a true pharmacogenomic effect. Although technically pre-planned, the subgroup analysis appears selectively emphasised and post hoc-enhanced to maximise statistical appeal.

For both the ITT and subgroup analyses, we cannot confirm whether the pooled dose comparisons were pre-specified, as the Statistical Analysis Plan (SAP) was conveniently not made public. If these pooled analyses were pre-defined and part of a pre-specified analytic framework, it would meaningfully increase confidence in the validity of the findings. However, in the absence of a public SAP, this cannot be verified, and the resulting lack of transparency raises legitimate concerns about selective reporting and statistical manipulation. It suggests a degree of smoke and mirrors in the presentation of efficacy.

D. Transparency and Reporting: A Pattern of Concern

The assessment of the Blarcamesine data package is severely hampered by a pattern of inadequate transparency and questionable reporting practices that fall well below the standards expected for a regulatory submission. These issues cast doubt on the integrity of the entire dataset and the analyses performed.

Undisclosed Statistical Analysis Plan (SAP): The sponsor has not made the SAP publicly available, despite it being standard practice for most published Phase 3 trials. The SAP is the cornerstone of trial integrity, as it prospectively defines all endpoints, analysis populations, statistical models, and multiplicity control strategies. Its absence makes it impossible for regulators to verify that the reported analyses were pre-specified and not the result of post-hoc data dredging or selective reporting.

Shifting P-values and Efficacy Estimates: There have been multiple, unexplained changes in the reported efficacy results over time. A press release from December 2022 reported an ADAS-Cog13 p-value of 0.033. A subsequent release in September 2023 cited a different effect size and p-value of 0.0226. The final publication reports a much lower p-value of 0.008. These material improvements in statistical significance, which conveniently moved the result across the $p < 0.025$ threshold, were not accompanied by any transparent explanation or documentation of changes to the analysis plan. This further raises serious concerns about potential "p-hacking" or undisclosed analytical flexibility.

Selective and Misleading Reporting of Endpoints: The sponsor's communication regarding the functional co-primary endpoint, ADCS-ADL, has been misleading. The initial December 2022 press release claimed a statistically significant functional benefit based on a non-standard, post-hoc responder analysis (Odds Ratio = 2.67, $p = 0.0255$). This was presented to suggest the trial was fully successful. However, the final publication revealed that the pre-specified continuous analysis for this endpoint failed unequivocally ($p = 0.357$). This practice of highlighting a favourable but non-prespecified analysis while downplaying or omitting the failure of the actual primary analysis is a form of selective reporting designed to obscure a negative result.

Data Inconsistencies: Unexplained internal discrepancies cast doubt on the reliability of the reported results. The CONSORT diagram reports 41 and 65 discontinuations due to adverse events (AEs) in the 30 mg and 50 mg blarcamesine groups, respectively, totalling 106 AE-related discontinuations **(Figure 3)**. However, the adverse events summary table (Table 3) lists 41 and 67 treatment-emergent adverse events (TEAEs) leading to treatment or study discontinuation in the same groups, totalling 108, a discrepancy of 2 patients. More concerningly, Supplementary Table 2, which breaks down AE-related discontinuations by scheduled visit window, accounts for only 74 such discontinuations across both blarcamesine groups from week 0 to week. This is 32–34 fewer events than reported elsewhere, a shortfall affecting $\sim 10\%$ of all patients treated. No explanation is provided for this discrepancy.

Figure 3. Inconsistencies in AE-Related Discontinuations Across CONSORT, AE Summary Table, and Visit-Based Discontinuation Reporting

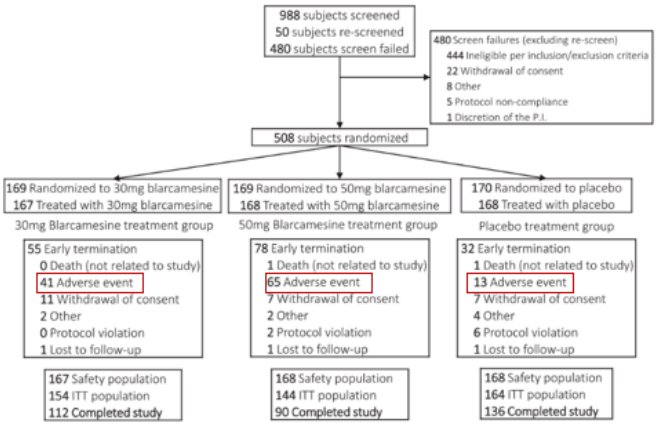


Fig. 1. Flowchart of patient screening, enrollment, discontinuation, and completion.

Table 3
Adverse events summary, full safety population.

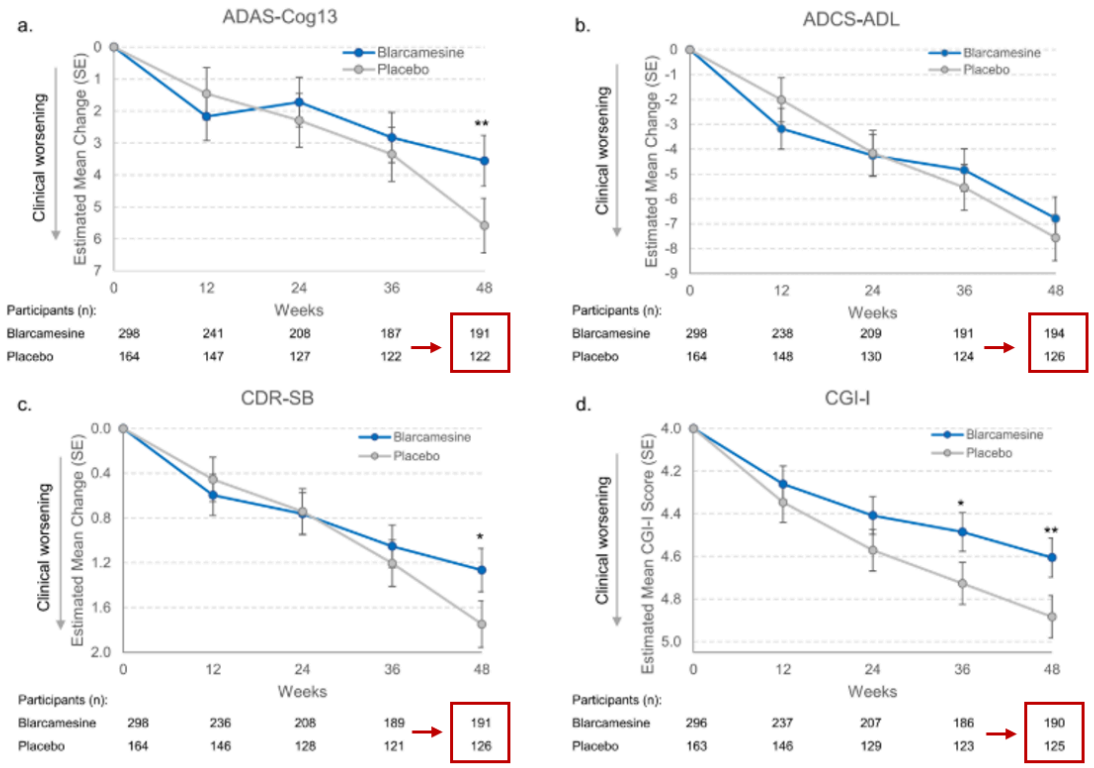
Adverse Events Summary	Blarcamesine 30 mg	Blarcamesine 50 mg	Blarcamesine	Placebo
Patients, n	167	168	335	168
Death, n (%)	0	1 (0.6)	1 (0.3)	1 (0.6)
Death considered related to treatment	0	0	0	0
Participants with ≥1 Serious TEAEs, n (%)	25 (15.0)	31 (18.5)	56 (16.7)	17 (10.1)
TEAE, n (%)	159 (95.2)	165 (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)

Discontinuations, by scheduled visit period, ITT population

Weeks	Blarcamesine (N = 96), n Disc. (%), n TEAE [% of Disc. due to TEAE]	Placebo (N = 28), n Disc. (%), n TEAE [% of Disc. due to TEAE]
0-12 *(Note: discontinued on or before reaching Week 12)*	40 (41.7%), 36 [90.0%]	5 (17.9%), 4 [80.0%]
13-24	32 (33.3%), 27 [84.4%]	11 (39.3%), 5 [45.5%]
25-36	16 (16.7%), 5 [31.3%]	7 (25%), 1 [14.3%]
37-48	8 (8.3%), 6 [75.0%]	5 (17.9%), 1 [20.0%]
TOTAL (0-48)	96 (100%), 74 [77.1%]	28 (100%), 11 [39.3%]

Even more troubling, the number of participants analysed at Week 48 exceeds those at Week 36, reversing the normal attrition trend and indicating intermittent missingness **(Figure 4).** Although a similar anomaly appeared in the phase 3 donanemab publication, it remains suspicious here because the study's only statistically significant cognitive effect also occurs precisely at Week 48, the time point most affected by these data inconsistencies.

Figure 4. Reversal of Expected Attrition Pattern: More Participants Analysed at Week 48 than Week 36 Across All Efficacy Endpoints



Collectively, these issues create a cloud of uncertainty around the trial's results. Without a transparent and verifiable account of how the data were analysed, we cannot have confidence in the robustness or validity of the efficacy claims.

V. Assessment of Biomarker and Mechanistic Evidence

A. Review of Fluid and Imaging Biomarkers: Failure to Confirm a Biological Effect

The EMA's 2018 guideline on Alzheimer's drug development emphasises the growing importance of biomarkers to provide objective evidence of a treatment's biological effect on the underlying pathophysiology of the disease. A robust biomarker package is crucial to support a claim of disease modification and to lend biological plausibility to clinical findings. The biomarker data submitted for Blarcamesine is weak, inconsistent, and ultimately fails to provide this necessary support.

The analysis of fluid biomarkers **(appendix Table 5A)** reveals a near-complete lack of effect on core disease processes:

- **Amyloid (A):** The sponsor reports a statistically significant increase in the plasma Aβ42/40 ratio for the combined Blarcamesine group versus placebo ($p=0.048$). However, this finding is unconvincing for several reasons. The p-value is marginal and would not survive any standard correction for

multiple testing (given that four key biomarkers were analysed). There is no clear dose-response, with the 50 mg group showing only a trend towards significance ($p=0.075$). The confidence interval for the combined group effect is narrow and touches zero (95% CI [0.000 to 0.026]), indicating a very weak and variable signal. Finally, changes in plasma Aβ42/40 are known to correlate poorly with clinical progression in Alzheimer's disease, making this a questionable surrogate for treatment effect.

- **Tau (T):** Critically, there was no statistically significant effect on the key plasma biomarkers of tau pathology, p-Tau181 ($p=0.39$) and p-Tau231 ($p=0.44$). In fact, p-Tau181 levels increased from baseline in both treatment arms. This is a major deficiency, as p-Tau is strongly linked to the formation of neurofibrillary tangles and correlates closely with cognitive decline. Approved anti-amyloid therapies like lecanemab and donanemab have demonstrated robust and highly significant reductions in p-Tau, confirming their downstream effect on tau pathology. Blarcamesine's failure to do so severs the link between its proposed mechanism and a core driver of Alzheimer's pathology.
- **Neurodegeneration (N):** Similarly, there was no significant effect on Neurofilament Light chain (Nf-L) ($p=0.28$), a sensitive marker of active axonal injury and neurodegeneration. While the increase in Nf-L was numerically smaller than in the placebo group, the lack of statistical significance means no conclusion of neuroprotection can be drawn. This again contrasts sharply with competitors like lecanemab, which showed highly significant reductions in Nf-L.

Although structural MRI showed a modest, statistically significant preservation of whole-brain and grey-matter volume, the result must be interpreted with great caution **(appendix Table 6A)**. MRI was mandated for every randomised participant at baseline, yet the annualised-change analysis drew only on a non-random subset of study completers. Inclusion was highest in the active arms—94 of 112 completers (83.9 %) in the 30 mg group and 72 of 90 (80.0 %) in the 50 mg group—versus 100 of 136 completers (73.5 %) in the placebo group. This imbalance introduces a serious risk of selection bias: patients who remained healthier and declined more slowly were more likely both to finish the trial and to appear in the MRI dataset, potentially inflating the apparent treatment effect. Accordingly, the reported slowing of brain-volume loss may reflect differential attrition rather than a genuine drug benefit. The table below will compare Blarcamesine’s limited biomarker signal with the stronger profiles of approved anti-amyloid therapies.

The following table compares Blarcamesine's weak biomarker profile to the established profiles of approved anti-amyloid therapies.

Table 6. Biomarker Outcomes for Blarcamesine vs. Approved Anti-Amyloid Therapies

Biomarker (A/T/N)	Blarcamesine	Anti-Amyloid mAbs (e.g., Lecanemab/Donanemab)	Regulatory Interpretation
Amyloid (A)	Marginal increase in plasma Aβ42/40 ($p=0.048$); no dose-response.	Highly significant amyloid plaque removal (PET) and CSF/plasma Aβ changes ($p<0.001$).	Blarcamesine signal is weak, unadjusted for multiplicity, and unconvincing.

Tau (T)	No significant effect on p-Tau181 or p-Tau231.	Robust, highly significant reductions in plasma p-Tau ($p < 0.001$).	Major failure for Blarcamesine; fails to show effect on a core AD pathology.
Neurodegeneration (N)	No significant effect on Nf-L. Modest MRI volume preservation in a biased subset.	Highly significant reduction in Nf-L ($p < 0.001$). Brain volume loss often accelerated (ARIA-A).	Blarcamesine fails to demonstrate a clear neuroprotective effect on validated markers.

In summary, the biomarker package fails to provide the necessary evidence to confirm a biological mechanism of action relevant to Alzheimer's disease. The absence of an effect on tau and neurodegeneration markers severely undermines both the clinical efficacy results and any claim of disease modification.

B. Mechanistic Plausibility: Novelty Weighed Down by High Risk

Blarcamesine's proposed mechanism of action is the activation of the sigma-1 receptor (SIGMAR1), a chaperone protein involved in cellular homeostasis, with additional activity as a muscarinic receptor modulator. While a novel mechanism can be an asset, particularly in a field with high rates of failure, it also carries a substantially higher burden of proof when the therapeutic pathway is not well-validated by the broader scientific community.

From a regulatory perspective, the SIGMAR1 pathway is considered high-risk. A review of the scientific literature on PubMed shows that research into SIGMAR1 in Alzheimer's disease is vastly underrepresented compared to the amyloid and tau pathways, and even inflammation. Furthermore, the clinical development history for compounds targeting related mechanisms is replete with failures. Pridopidine, another S1R agonist, failed multiple late-stage trials in Huntington's disease and Parkinson's disease. Numerous muscarinic and cholinergic modulators, such as xanomeline, talsaclidine, and intepirdine, have also failed in large Alzheimer's trials.

Adding to these concerns is Blarcamesine’s late-stage failure in its Rett-syndrome program, a neurodevelopmental disorder that was considered a mechanistically rational target for the drug. The program failed due to a combination of a definitive clinical trial failure and a pattern of questionable scientific methodology that undermined its credibility. This failure raises significant questions about the translatability of the proposed mechanism and the viability of the platform, as well as the transparency of the data.

Without strong, consistent, and replicated clinical data supported by a robust biomarker package, a novel mechanism like SIGMAR1 activation is viewed by regulators not as a breakthrough, but as an unproven and high-risk hypothesis. The weak and inconsistent data package for Blarcamesine fails to provide the necessary evidence to de-risk this novel mechanism and establish its therapeutic relevance in Alzheimer's disease.

VI. Regulatory & Legal Risk Assessment

A. Regulatory Strategy Red Flags

The sponsor's regulatory strategy provides further cause for concern. An unusual 14-month delay occurred between the top-line data readout (December 2022) and the MAA submission to the EMA (Q1 2024). In a high-unmet-need indication like Alzheimer's, compelling data typically leads to swift regulatory filings. This delay may suggest difficulties in assembling a coherent data package or unresolved regulatory or manufacturing issues.

Even more telling is the complete absence of a concurrent submission to the U.S. Food and Drug Administration (FDA) and the fact that the pivotal trial included no U.S. clinical sites. Given the size of the U.S. market and the FDA's recent flexibility in approving Alzheimer's therapies, even those with ARIA, this strategic omission is highly atypical, suggesting a poor investment or a lack of confidence from the sponsor in the data's ability to withstand rigorous regulatory scrutiny.

B. Litigation History & Allegations of Data Manipulation

The legal complaint dated March 13, 2024, filed by LEVI & KORSINSKY LLP provides highly critical statistical details, arguing a pattern of deception began with the adult AVATAR study. It alleges that after establishing study measures in May 2019, Anavex abruptly changed its primary endpoints on January 18, 2022, just two weeks before releasing the results. This change involved using the CGI-I score as an "anchor" for a new endpoint, a metric CEO Christopher Missling had previously dismissed as "weak", while the supposedly *"more rigorous endpoin*t", the RSBQ, was now presented as needing this anchor. Analysts immediately expressed confusion; Charles Duncan of Cantor Fitzgerald wrote on February 1, 2022, that *"we cannot say clinical proof-of-concept has been established*" without "*well-defined approvable endpoints*" and found the company's execution "*confounding*". Consequently, despite claims of success, Anavex's stock fell 19.3%, from $13.08 on January 31, 2022, to $10.55 on February 2, 2022. The complaint alleges this "same sleight of hand" was repeated with the pediatric EXCELLENCE study, for which Missling had explicitly promised to "use the same endpoint" as AVATAR. Instead, the company used a different "MMRM" method not seen in AVATAR, failed to report the AVATAR endpoint (RSBQ AUC), and ultimately failed to meet its co-primary endpoint, the CGI-I score. Anavex blamed this failure on a "large placebo effect", and Missling later claimed the study was "not fully powered", despite previously exceeding enrollment targets. This news triggered a 35% collapse in stock price in one day, from $9.31 on December 29, 2023, to $6.05 on January 2, 2024.

VI. Overall Conclusion and Outlook

A. Final Recommendation Justification

Based on the totality of the evidence, the benefit-risk profile for Blarcamesine is judged to be unequivocally negative. The modest, fragile, and methodologically compromised evidence of a cognitive benefit does not outweigh the risks associated with poor tolerability and, more critically, the profound uncertainties surrounding the validity and integrity of the data itself.

Despite the high unmet need, the convenience of an oral therapy, and the absence of ARIA events, the publicly available data fails to provide the robust and consistent evidence required for marketing authorisation and the sponsor’s slow EMA filing signals, together with ongoing litigation, further limit confidence and erode trust in the integrity of the evidence base.

The CHMP's recent negative opinion in March 2025 on donanemab, a drug with a much larger and more statistically robust dataset, underscores the high evidentiary bar in Europe, particularly regarding the need for a clear and favourable benefit-risk balance. The Blarcamesine data package falls far short of this standard.

Therefore, the recommendation is to refuse the granting of a marketing authorisation. The applicant would need to conduct a second, large, well-controlled, and prospectively designed confirmatory Phase 3 trial to address the manifold deficiencies identified in this assessment. Such a trial would need to demonstrate a statistically persuasive and clinically meaningful effect on co-primary endpoints of cognition and function, be supported by robust biomarker data, and be conducted with the highest standards of transparency and data integrity before this product could be reconsidered for full or conditional approval.

B. When Will The CHMP Opinion Announcement Happen?

Anavex Life Sciences' application for its drug blarcamesine is currently undergoing a comprehensive review by the European Medicines Agency (EMA), a process that began on December 23, 2024. The EMA's scientific committee (CHMP) takes over approximately 210 active days to evaluate. However, this timeline may be extended by procedural 'clock stops,' where the review is paused while the CHMP awaits additional information from the company. Factoring in these potential delays, a formal opinion is anticipated anytime from July 21, 2025, and will be adopted during one of the CHMP's scheduled monthly meetings.

Following the committee's vote on the last day of the meeting, Anavex will receive immediate and confidential notification of the outcome. The public announcement follows later, typically in a 'meeting highlights' summary released on the EMA website the following week. This CHMP opinion serves as a recommendation to the European Commission, which then has approximately 67 days to issue a final, legally binding decision - a recommendation they almost always follow.

Assuming a standard review that includes one or two clock stops of a typical duration (a cumulative 2-3 months), the total review time would align with a standard 9-10-month timeframe. This makes the September 18 and October 16 meetings, or the days immediately following them, the most likely candidates for a final CHMP opinion on blarcamesine.

Given the totality of public evidence and regulatory precedent, it is reasonable to anticipate that Anavex will receive a negative CHMP opinion. In such a scenario, the company is likely to issue a statement on the next business day (e.g., Friday) or possibly the following Monday morning. This short delay would allow internal teams time to review the opinion in detail, determine whether to pursue re-examination, and craft a controlled narrative for investor relations and damage mitigation.

C. Cash-Floor Reality: How a Negative CHMP Verdict Could Reprice AVXL

As of this report dated July 13, 2025, Anavex Life Sciences (NASDAQ: AVXL) is trading at US $11.11 per share.

Anavex ended Q1 2025 with US $115.8 million in cash and 83.9 million shares outstanding, placing its theoretical liquidation floor at approximately US $1.38 per share. While this figure represents a book-value baseline, the market’s reaction to a regulatory decision will be shaped by broader dynamics, including prevailing sentiment, short positioning, and perceived pipeline value. As of July 2025, short interest remains elevated at over 25 million shares, representing around 33% of the float, with a days-to-cover ratio exceeding 26, indicating substantial bearish pressure.

When the CHMP issues a negative opinion on blarcamesine, an algorithm-driven headline sell-off will likely exceed >70%, at least in the opening hours of trading. Even so, the stock would likely find support above pure cash value; applying a very modest two-times multiple to cash to reflect residual pipeline optionality suggests a near-term stabilisation around or less than US $2.8 per share.

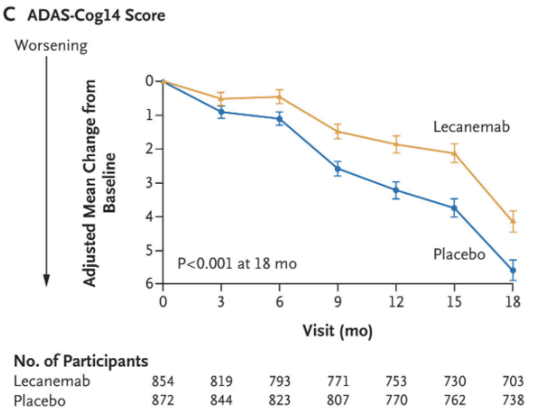
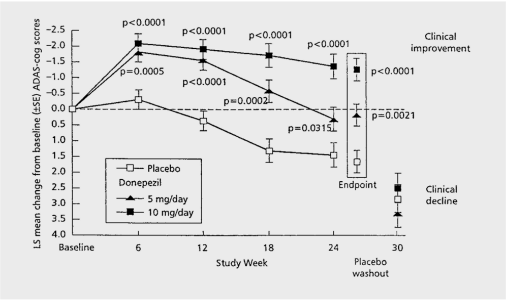
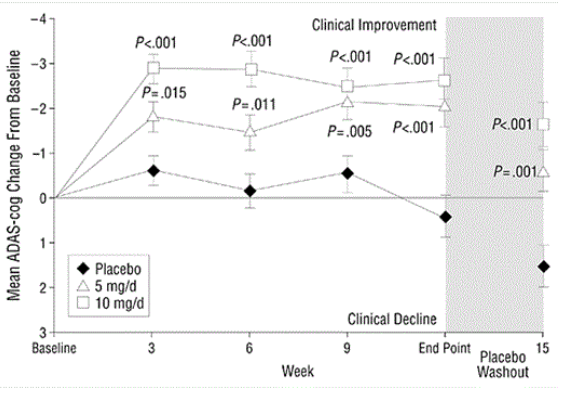
The scale of the decline will hinge on the tone of the CHMP summary, which is expected to emphasise failure to meet efficacy endpoints, label the dataset unreliable because of significant methodological flaws, and note poor tolerability driven by dizziness and confusional states. Although it may also acknowledge the absence of ARIA or overt organ toxicity, any reference to signals in SIGMAR1 wild-type patients will be recognised as hypothesis-generating only, not grounds for approval.

Such wording would inflict a serious credibility blow. A formal declaration that the evidence cannot be trusted would leave Anavex on the back foot with regulators and investors alike. The most constructive advice the agency could offer is a fresh, genotype-stratified Phase 3 trial, an endeavour that would require major capital, several years, and effectively reset the Alzheimer's programme.

Management will doubtless try to reframe the decision as a "delay" rather than a failure, echoing its messaging after the Rett-syndrome disappointment. In practice, however, the Alzheimer's programme is likely to be shelved or quietly wound down while resources shift to earlier-stage assets. In short, a negative CHMP opinion would drive the share price toward cash-backed levels, with only a modest premium left to account for whatever optionality remains in the rest of the pipeline.

VII. Appendix

Table 1A. Benchmark ADAS-Cog Treatment Effects in Approved Alzheimer's Therapies

Lecanemab (Mild AD / MCI due to AD) Van Dyck et al. 2022	−1.44 (95% CI, −2.27 to −0.61; P < 0.001)	18 months	Early and sustained statistically significant separation from placebo to end of trial (P < 0.001). 
Donepezil 10mg (mild to moderate AD) Burns et al. 1999	-2.9	24 weeks LOCF	Early and sustained statistically significant separation from placebo to end of trial (P < 0.001). 
Donepezil 10mg (mild to moderate AD) Rodgers et al. 1998	- 3.1 95% CI: (−4.30,−1.90) - calculated	12 weeks LOCF	Early and sustained statistically significant separation from placebo to end of trial (P < 0.001). 

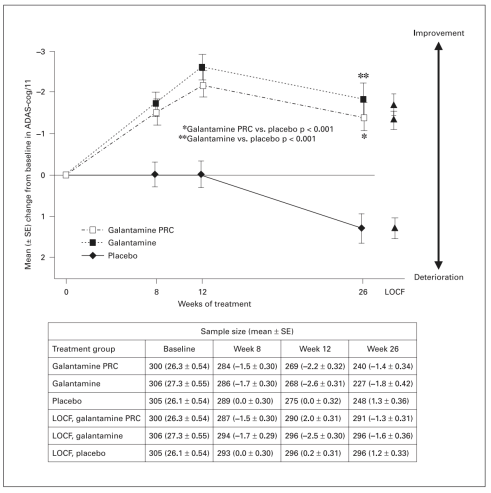
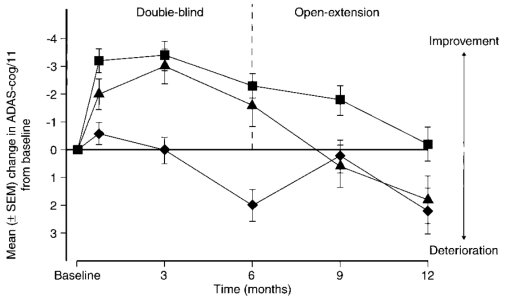
Galantamine 8 or 12 mg twice daily (pooled) (mild to moderate AD) Brodaty et al. 2005	-2.8 (95% CI, −3.70 to −1.86)	26 weeks LOCF	Early and sustained statistically significant separation from placebo to end of trial.  Sample size (mean ± SE) Treatment group / Baseline / Week 8 / Week 12 / Week 26 Galantamine PRC: 300 (26.3 ± 0.54) / 284 (−1.5 ± 0.30) / 269 (−2.2 ± 0.32) / 240 (−1.4 ± 0.34) Galantamine: 306 (27.3 ± 0.55) / 286 (−1.7 ± 0.30) / 268 (−2.6 ± 0.31) / 227 (−1.8 ± 0.42) Placebo: 305 (26.1 ± 0.54) / 289 (0.0 ± 0.30) / 275 (0.0 ± 0.32) / 248 (1.3 ± 0.36) LOCF, galantamine PRC: 300 (26.3 ± 0.54) / 287 (−1.5 ± 0.30) / 290 (2.0 ± 0.31) / 291 (−1.3 ± 0.31) LOCF, galantamine: 306 (27.3 ± 0.55) / 294 (−1.7 ± 0.29) / 296 (−2.5 ± 0.30) / 296 (−1.6 ± 0.36) LOCF, placebo: 305 (26.1 ± 0.54) / 293 (0.0 ± 0.30) / 296 (0.2 ± 0.31) / 296 (1.2 ± 0.33) **Fig. 2.** Mean change (±SEM) from baseline in (ADAS-cog/11) score over time (intent-to-treat analysis set).
Galantamine 32 mg/d group (mild to moderate AD) Raskind et al. 2000	-3.4 (95% CI of (-4.63 to -2.17)	6 months LOCF	Early and sustained statistically significant separation from placebo to end of trial.  *Figure 2. Mean change from baseline in 11-item AD Assessment Scale cognitive subscale (ADAS-cog/11) scores over 12 months (observed cases analysis). ■ = Galantamine 24 mg/galantamine 24 mg; ▲ = galantamine 32 mg/galantamine 24 mg; ◆ = placebo/galantamine 24 mg.*

Figure 1A. Observed Week 12 Outcomes in ITT Completers, which Excluded Post-Week 12 Dropouts

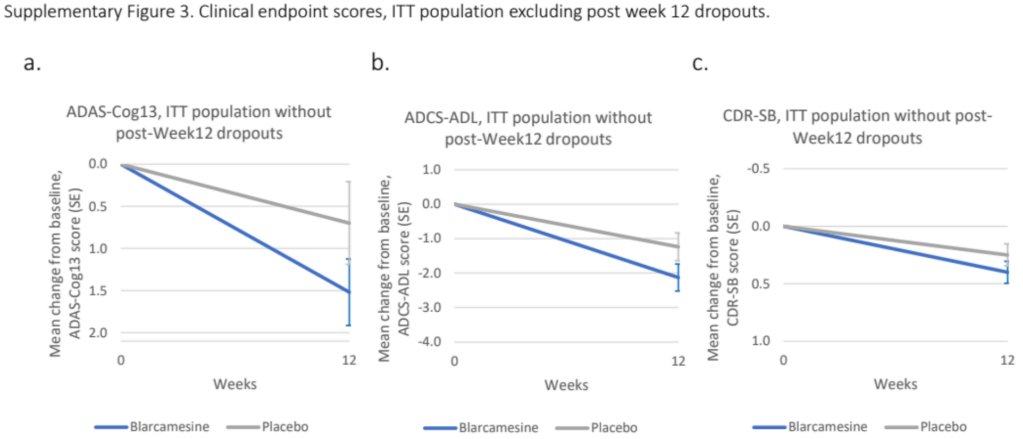


Table 2A. Pooling of Dose Arms Yields Stronger Endpoints at Week 48 Despite Marginal Individual Results, SIGMAR1 rs1800866 Variant Non-Carrier Subgroup

Supplemental Table 5. Primary and Secondary End Points, SIGMAR1 rs1800866 Variant Non-Carrier Subgroup					
	Individual Group Comparison			Group Comparison	
	Blarcamesine 30 mg (N = 106)	Blarcamesine 50 mg (N = 93)	Placebo (N = 101)	Blarcamesine (N = 199)	Placebo (N = 101)
Primary efficacy endpoints					
Change from baseline to week 48 in the **ADAS-Cog13** score					
No. of participants at week 48	81	56	81	137	81
Adjusted mean change	2.384	2.329	4.686	2.340	4.657
Adjusted mean difference vs. placebo (95% CI)	-2.302 (-4.398 to -0.206)	-2.357 (-4.656 to -0.058)	..	-2.317 (-4.182 to -0.453)	..
P value vs. placebo	0.031*	0.045*	..	0.015*	..
Less decline, %	49.1%	50.3%	..	49.8%	..
Change from baseline to week 48 in the **ADCS-ADL** score					
No. of participants at week 48	81	58	85	139	85
Adjusted mean change	-5.865	-6.506	-6.867	-6.171	-6.898
Adjusted mean difference vs. placebo (95% CI)	1.002 (-1.205 to 3.209)	0.361 (-2.058 to 2.779)	..	0.727 (-1.230 to 2.683)	..
P value vs. placebo	0.373	0.770	..	0.466	..
Less decline, %	14.6%	5.3%	..	10.5%	..
Secondary efficacy endpoint Change from baseline to week 48 in the **CDR-SB** score					
No. of participants at week 48	80	57	85	137	85
Adjusted mean change	1.150	1.216	1.782	1.184	1.785
Adjusted mean difference vs. placebo (95% CI)	-0.632 (-1.160 to -0.104)	-0.565 (-1.145 to 0.014)	..	-0.601 (-1.070 to -0.133)	..
P value vs. placebo	0.019*	0.056	..	0.012*	..
Less decline, %	35.5%	31.8%	..	33.7%	..
Exploratory endpoint Improvement from baseline to week 48 in the **CGI-I** score					
No. of participants at week 48	79	57	84	136	84
Adjusted improvement	4.544	4.502	4.782	4.527	4.783
Adjusted mean difference vs. placebo (95% CI)	-0.238 (-0.495 to 0.018)	-0.280 (-0.560 to 0.000)	..	-0.256 (-0.483 to -0.030)	..
P value vs. placebo	0.069	0.0497*	..	0.027*	..
Less decline, %	5.0%	5.9%	..	5.4%	..

Table 3A. Pooling of Dose Arms Yields Stronger Endpoints at Week 48 Despite Marginal Individual Results

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%	..

Table 4A. Discontinuations, by scheduled visit period, ITT population

Weeks	Blarcamesine (N = 96), n Disc. (%), n TEAE [% of Disc. due to TEAE]	Placebo (N = 28), n Disc. (%), n TEAE [% of Disc. due to TEAE]
0-12 (*Note: discontinued on or before reaching Week 12)*	40 (41.7%), 36 [90.0%]	5 (17.9%), 4 [80.0%]
13-24	32 (33.3%), 27 [84.4%]	11 (39.3%), 5 [45.5%]
25-36	16 (16.7%), 5 [31.3%]	7 (25%), 1 [14.3%]
37-48	8 (8.3%), 6 [75.0%]	5 (17.9%), 1 [20.0%]

Figure 2A. Discontinuations, by scheduled visit period, ITT population

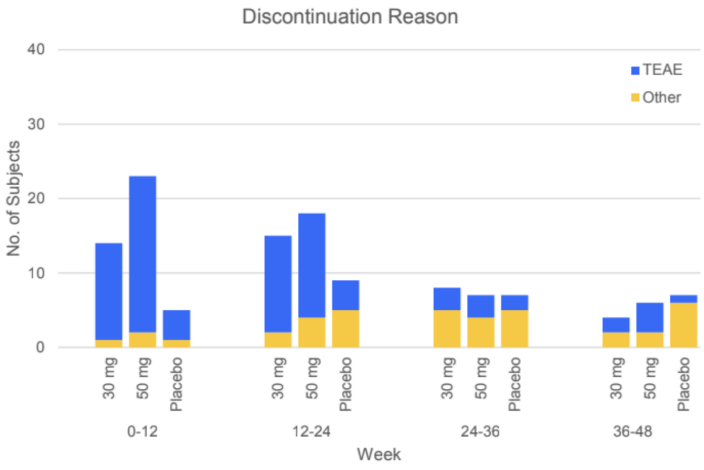


Table 5A. Plasma Biomarker Levels, changes from baseline at 48 weeks

Supplementary Table 3. Plasma biomarker levels, change from baseline at 48 weeks, ITT population

Plasma Biomarker Endpoints	Blarcamesine 30 mg (n = 154)	Blarcamesine 50 mg (n =144)	Blarcamesine Group (n = 298)	Placebo (n = 164)
Change from baseline to week 48, Aβ42/40 ratio				
No. of participants evaluated	67	52	119	78
Mean change (SD)	+0.006 (0.028)	+0.021 (0.080)	+0.013 (0.057)	−0.0003 (0.035)
Mean difference vs. placebo (95% CI)	0.007 (-0.004 to 0.017)	0.021 (-0.002 to 0.045)	0.013 (0 to 0.026)	--
P value vs. placebo	0.206	0.075	0.048*	--
Change from baseline to week 48, Nf-L				
No. of participants evaluated	99	83	182	122
Mean change (SD), pg/mL	+1.38 (6.54)	+1.96 (6.88)	+1.65 (6.68)	+4.92 (33.00)
Mean difference vs. placebo (95% CI)	-3.54 (-9.59 to 2.51)	-2.96 (-9.05 to 3.13)	−3.28 (−9.27 to 2.72)	--
P value vs. placebo	0.25	0.34	0.28	--
Change from baseline to week 48, p-Tau (181)				
No. of participants evaluated	92	73	165	117
Mean change (SD), pg/mL	+2.92 (14.17)	+5.17 (16.33)	+3.92 (15.16)	+10.85 (85.63)
Mean difference vs. placebo (95% CI)	-7.92 (-23.86 to 8.02)	-5.67 (-21.78 to 10.44)	-6.93 (-22.77 to 8.92)	--
P value vs. placebo	0.33	0.49	0.39	--
Change from baseline to week 48, p-Tau (231)				
No. of participants evaluated	50	55	105	83
Mean change (SD), pg/mL	+2.27 (13.54)	-1.51 (12.08)	+0.29 (12.87)	+3.86 (40.66)
Mean difference vs. placebo (95% CI)	-1.59 (-11.21 to 8.04)	-5.37 (-14.79 to 4.05)	-3.57 (-12.77 to 5.63)	--
P value vs. placebo	0.74	0.26	0.44	--

Plasma samples were taken at baseline and 48 weeks for quantification of protein biomarkers. Statistical significance was evaluated by an unpaired two-tailed t-test comparison of the two groups, with a significance threshold of $P < 0.05$ (*). Patient numbers in each treatment group represent patients with both baseline and end of study results for each measurement; for Aβ42/40 ratio, the number includes patients with baseline and end of study results for both Aβ42 and Aβ40.

Table 6A. Volumetric MRI measurements, changes from baseline at 48 weeks

Supplementary Table 4. Volumetric MRI measurements, annualised percent change from baseline, general linear model, ITT population

MRI Measurement	Individual Group Comparison			Combined Group Comparison	
	Blarcamesine 30 mg (n = 154)	Blarcamesine 50 mg (n =144)	Placebo (n = 164)	Blarcamesine Group (n = 298)	Placebo (n = 164)
Whole Brain, %change from baseline					
Number of subjects	93	72	100	165	100
Adjusted mean change (SE)	-1.14% (0.23)	-1.45% (0.26)	-2.04% (0.23)	-1.27% (0.19)	-2.04% (0.23)
Adjusted mean difference vs. placebo (95% CI)	0.9% (0.35 to 1.44)	0.59% (0.00 to 1.18)		0.77% (0.29 to 1.25)	--
P value vs. placebo	0.001**	0.049*		0.002**	--
Total Grey Matter, %change from baseline					
Number of subjects	94	72	100	166	100
Adjusted mean change (SE)	-0.62% (0.44)	-1.05% (0.50)	-2.18% (0.44)	-0.80% (0.37)	-2.18% (0.44)
Adjusted mean difference vs. placebo (95% CI)	1.56% (0.52 to 2.61)	1.13% (0.00 to 2.26)		1.38% (0.46 to 2.3)	--
P value vs. placebo	0.003*	0.049*		0.004**	--
Total White Matter, %change from baseline					
Number of subjects	93	72	100	165	100
Adjusted mean change (SE)	-2.01% (0.39)	-1.94% (0.44)	-1.89% (0.39)	-1.98% (0.33)	-1.89% (0.38)
Adjusted mean difference vs. placebo (95% CI)	-0.12% (-1.04 to 0.81)	-0.05% (-1.05 to 0.95)		-0.09% (-0.9 to 0.73)	--
P value vs. placebo	0.806	0.919		0.832	--
Lateral Ventricles, %change from baseline					
Number of subjects	94	72	100	166	100
Adjusted mean change (SE)	8.76% (0.79)	7.07% (0.89)	10.74% (0.78)	8.06% (0.67)	10.76% (0.78)
Adjusted mean difference vs. placebo (95% CI)	-1.97% (-3.84 to -0.1)	-3.66% (-5.67 to -1.65)		-2.70% (-4.36 to -1.05)	--
P value vs. placebo	0.039*	<0.001***		0.002**	--