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Letter to the Editor

Concerns about Anavex's clinical trial of Blarcamesine

Dear Editor,

I am writing to express my concerns regarding the recent publication, "*Blarcamesine for the Treatment of Early Alzheimer's Disease: Results from the ANAVEX2–73-AD-004 Phase IIB/III Trial.*" I believe there are several troubling aspects to this report, including:

1. The characterization of the findings as robust.
2. An inconsistent history of reporting results by the sponsor, Anavex Life Sciences.
3. The failure to make the protocol and statistical analysis plan available to readers.

1. Tipping point analysis concern

The sensitivity analysis employed in this study was a tipping point analysis and is presented in supplemental Table 7. The result for the tipping point of the blarcamesine group was a worsening of 1.9 points. The authors argue in the text that this supports the robustness of the findings on the primary endpoint; however, I believe this is a misunderstanding of how tipping point analyses measure robustness. Robustness is indicated by how clinically implausible a tipping point would need to be for the observed results to lose significance [1]. In this case, the tipping point is still better than placebo (1.973 worse) and is therefore entirely plausible. An implausible tipping point, by contrast, would, at the very least, be worse than placebo. Frankly, the description "As the observed treatment difference is −1.973, this result supports the robustness of the MAR assumption in the primary analysis" is bizarre and, in my opinion, exactly the opposite is true. I have included a graphical comparison with Lecanemab to illustrate my point.

2. Inconsistent reporting of results

Secondly, the results of this trial were first presented by the sponsor more than 2 years ago at CTAD 2022, with different values for the effect than is contained in the current report (−1.85 and/or −1.34 compared to the current −2.027). In September of 2023, the sponsor presented yet another value for the difference in ADAS-Cog13 scores (−1.783, [2]). While allowances for various exploratory analyses of data should be tolerated, prespecified analysis of the primary endpoint on the ITT population (as all these were described) should not change over presentations. To preempt any glib dismissal of these prior reports, I note that the −1.85 and −1.73 values were filed by the sponsor with the SEC in accordance with the Sarbanes-Oxley Act as "accurate and not misleading." Although the authors have argued on Pubpeer.com [3] that historical numbers presented by the sponsor are beyond the scope of the current publication, the fact that the sponsor was responsible for the "collection, management, analysis, and interpretation of the data" in the current report raises questions about which analysis was prespecified and/or the competence of the sponsor that are directly relevant to the current publication.

3. Protocol and statistical analysis plan

Lastly, it is customary to provide the clinical trial protocol and statistical analysis plan when reporting phase III Alzheimer's Disease clinical trial results, including in this journal [4]. Despite this and repeated requests on Pubpeer.com, the authors have thus far declined to provide those documents. Given the issues outlined above and the broader skepticism currently surrounding Alzheimer's research (e.g. Doctored: Fraud, Arrogance, and Tragedy in the Quest to Cure Alzheimer's, by Charles Piller, *in press*), I respectfully request that the authors follow standard practice by sharing the trial protocol and statistical analysis plan, explain the inconsistent history of the trial results and change the characterization of the tipping point result to reflect that the results are not robust. Doing so would be beneficial not only for the journal and its readership but also for the Alzheimer's research community. There is some urgency regarding these matters as the sponsor has indicated that they have submitted blarcamesine to the EMA for marketing authorization.

Sincerely,

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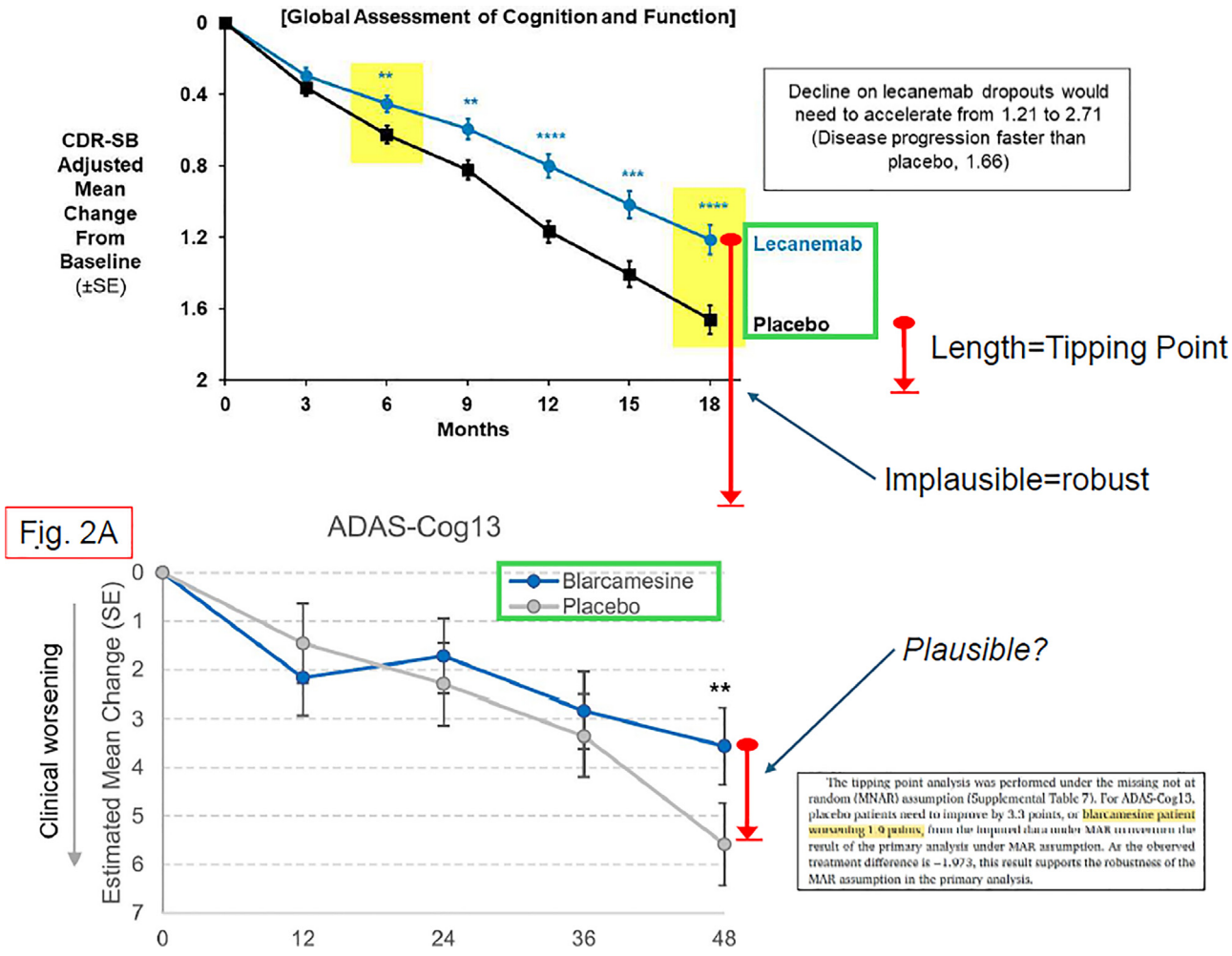

The upper graph, taken from the Lecanemab AdComm presentation in 2023 [5], and the lower graph, Figure 2A from the current report, both show red arrows I inserted marking the tipping points (with text boxes quoting the source). In each case, the length of the arrow corresponds to the reported tipping point.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jesse Brodkin reports was provided by Behavioral Instruments. Jesse Brodkin reports a relationship with Behavioral Instruments that includes: employment. Previous short stock position in the Sponsor, but The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Jesse Brodkin: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100137.

References

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[5] https://www.fda.gov/media/169338/download. 2023.

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