Evaluate Vantage

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Subgroup data no balm for Biogen/Eisai Alzheimer's drug

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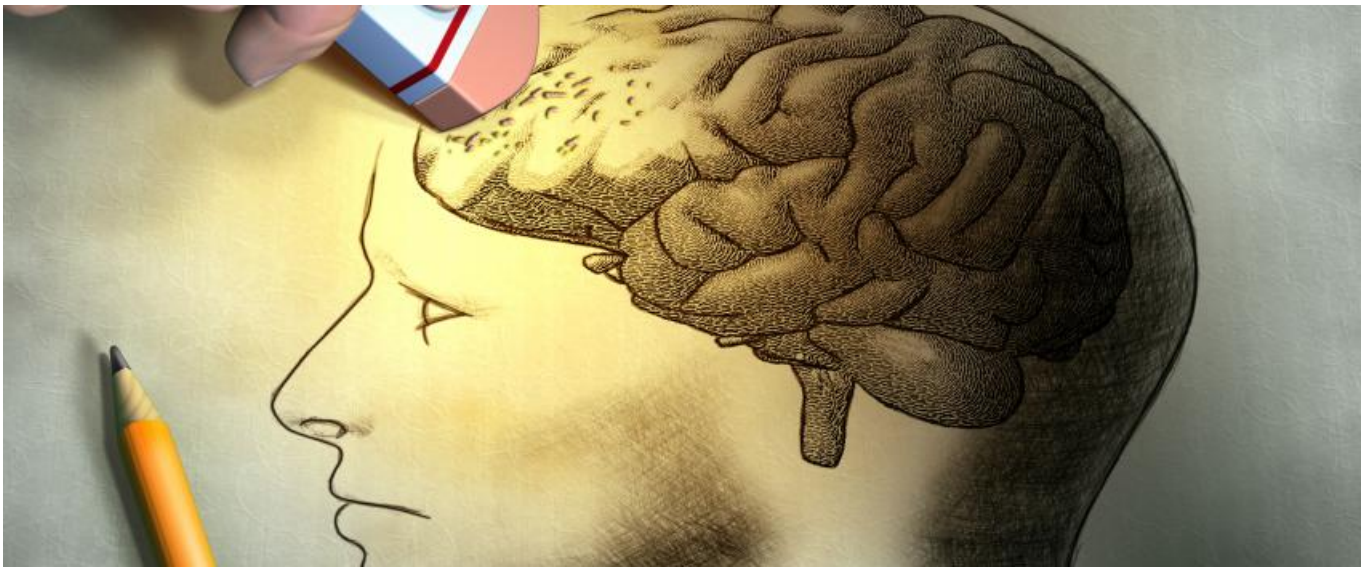

BAN2401 may work better in genetically defined population, but with safety risks.

Finding a therapeutic window for Biogen and Eisai's Alzheimer's disease project BAN2401 will be difficult at best. Detailed subgroup data from study 201 show that the best responding patients at the highest dose are at greater risk of brain swelling, while patients outside this group see only mixed benefits.

That the partners have not expressed confidence that BAN2401 will move into advanced trials could be taken as a sign of how disappointing the results were. Yet since this is Alzheimer's, where even underwhelming pivotal results cannot kill some agents, BAN2401 could still survive this setback.

Better in carriers

The new data concern exploratory 18-month analyses from study 201, which compared several doses of BAN2401, an anti-amyloid beta antibody, against placebo. Specifically, Biogen and Eisai released at the CTAD meeting in Barcelona further examination of patients with the APOE4 mutation, a marker for rapid cognitive decline.

It should be remembered that the trial missed its primary endpoint, so at best these findings are hypothesis-generating.

At the Alzheimer's Association International Conference meeting in July, the partners released a data set that included APOE4 carriers in the placebo arm, but excluded them from the BAN2401 arm at 10mg/kg every other week, the highest dose, effectively enriching the intervention arm with patients expected to perform better (*Full BAN2401 reveal gives Biogen a reality check, July 26, 2018*). This was done, the partners said, because concerns about a brain swelling side effect meant that they had to stop randomising APOE4 carriers into this highest dose.

The good news in the new data, from Biogen and Eisai's perspective, is that the APOE4 carriers in that 10mg/kg group scored better than carriers in the placebo group on three endpoints: the composite measure ADCOMS, ADAS-COG, and CDR-SB. That means that the benefit seen in the earlier analysis was not driven by the imbalance between APOE4 carriers in the two arms.

The bad news is that in non-carriers, even this high dose of BAN2401 looks little better than placebo – in fact it was numerically worse than placebo on CDR-SB.

Moreover, the data in carriers comes from just 10 patients thanks to a request from EU regulators to stop randomising APOE4 patients to that highest dose because of a safety signal called amyloid-related imaging abnormalities (ARIA-E), a sign of cerebral oedema. Given the ARIA-E rate of 14.6% in the 10mg/kg group, that is not too surprising, and certainly is another knock for BAN2401.

Proof of concept, or not

While some bullish investors were willing to regard this analysis as constituting proof of concept to support a phase III trial, Biogen and Eisai themselves were more circumspect. A joint press release said the two are "currently discussing the next steps for BAN2401 with regulatory authorities" – a far cry from the usual biopharma approach of talking up a pivotal trial.

In a call with analysts yesterday, Biogen executives declined to comment because of the regulatory interactions. They did say they do not expect that because of ARIA-E worries APOE4 carriers would be excluded from a phase III trial, should one happen.

In one sense, the BAN2401 bulls are correct. Other than the mixed and nearly uninterpretable data set presented here, Biogen and Eisai have been given no clear signal to terminate work – after all, it took three pivotal failures for Eli Lilly to pull the plug on solanezumab, and even now university researchers continue to work with the antibody (*Preventive Alzheimer's trials keep amyloid hope alive, April 26, 2018*).

Nonetheless, these results are far from a rousing validation of BAN2401, and it would be a surprise if regulators back phase III work based on study 201. But do not expect Biogen and Eisai to give up, either. With so much to play for in Alzheimer's, they will probably view it as a risk worth taking.