Evaluate Vantage

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Biogen’s aducanumab heads for US approval

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Briefing documents on the Alzheimer’s project are shot through with enthusiasm, and render statistical rigor a minor consideration.

The bull case for Biogen’s beta-amyloid Alzheimer’s antibody aducanumab had been that one controversially cherrypicked pivotal study out of two was enough to support approval, though probably not at first pass. Until yesterday, that is.

US FDA briefing documents have revealed just how supportive the agency is of not just one but both trials, and suggested that the impetus to reanalyse the findings had come from the FDA. With aducanumab now looking like a shoo-in for first-pass approval Biogen stock put on an incredible 44%, or $17bn of valuation uplift.

The documents were published yesterday, in preparation for an advisory committee meeting due to debate aducanumab’s filing tomorrow. With the FDA apparently moving heaven and earth to stretch statistical methodology to breaking point, it will come as no surprise that virtually the only dissenting voice in the documents came from its statistical reviewer.

Studies terminated

The adcom is being asked to scrutinise three trials: Emerge (Study 302), Engage (Study 301), both pivotal, and Prime (Study 103), a small phase I test.

All three had been terminated for futility back in March 2019. But, as has been widely documented, Biogen later claimed that its futility analysis had been incorrect, and that with longer follow-up Engage was shown to be positive for aducanumab’s higher, 10mg/kg dose (*Shock revelation sees Biogen erase its aducanumab losses, October 22, 2019*).

The briefing documents reveal that it was the FDA that pushed for this reanalysis; at a June 2019 meeting the agency stated that “it would have been more appropriate if futility had not been declared for those studies”.

It was the agency that asked Biogen to “provide conditional power estimates if non-pooled futility analyses had been performed for each study independently”. And four months later the FDA said analyses had suggested why Emerge and Engage had yielded “discordant” results, and that just the former might back approval.

The enthusiasm reaches fever pitch in the agency’s summary position on the Emerge trial: “FDA agrees that the results of Study 302 are highly persuasive... Study 302 is a strongly positive study on multiple distinct and important clinical measures.”

Moreover, the failed trial looks also to have been datadredged for supportive signs. While agreeing that Engage was “negative”, the agency zeroes in on rapid progressers, in which an even small imbalance “can have a relatively large impact... The high-dose arm in Study 301 was disproportionately affected by such an imbalance.”

“When the small number of rapid progressers are removed, the point estimate of the treatment effect for the high dose in Study 301 favours aducanumab,” the FDA gushes, adding that this finding is “consistent with every other treatment arm across the aducanumab development programme”.

Meanwhile, Prime, a study with only 30 subjects in its high-dose arm, is cited as providing supportive evidence.

Criticism

A sign of how much the debate has swung in Biogen’s favour is that the CDR-SB score, Emerge and Engage’s primary measure, is barely criticised. Only a few years ago CDR-SB was seen merely as a general tool doctors used to assess a patient initially, and had no relevance as a study endpoint.

It is only in an appendix starting on page 247 of the 343-page document that the mathematical gymnastics the agency has used to extrapolate aducanumab’s benefits face a grilling, from Tristan Massie, a statistical reviewer.

He is scathing, arguing that the data show “much inconsistency and no replication. There is only one positive study at best, and a second study which directly conflicts with the positive study.” He also cites a significantly worse incidence of falls with the high aducanumab dose, an apparently fresh concern.

A new trial, fully completed according to protocol without post hoc amendments, is called for to confirm the purported effect.

Tomorrow’s discussion will be fascinating. The FDA is not bound to follow the advice of an advisory panel, and indeed the briefing documents are merely advice for the adcom. But it is hard not to see aducanumab being approved now.

Voting questions for the Nov 6 aducanumab adcom (summarised)	
1	Does the Emerge trial, viewed independently from Engage, provide strong evidence that supports aducanumab's effectiveness?
2	Does the Prime trial provide supportive evidence of aducanumab's effectiveness?
3	Has Biogen presented strong evidence of a pharmacodynamic effect on Alzheimer’s disease pathophysiology?
4	Is it reasonable to consider Emerge as primary evidence of aducanumab's effectiveness?
Source: US FDA.	