

## The recent aducanumab announcement by Biogen: a dramatic turning point for the Alzheimer's disease community

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- **Biogen announced additional data now indicate that aducanumab is effective in patients with longer term, high-dose exposure, and that they plan to file a marketing application with FDA early next year**
- **The clinical findings support the amyloid hypothesis of a pathogenic role for beta-amyloid aggregates in Alzheimer's disease**
- **Clinical benefit is dependent on the amount of antibody reaching the pathogenic species (toxic beta-amyloid oligomers), but higher doses cannot be safely achieved with aducanumab due to the risk of ARIA-E (brain swelling) associated with plaque binding**
- **There is still a need for a next-generation therapeutic that selectively targets oligomers in order to achieve greater safety and efficacy**

**Background for the aducanumab announcement:** Biogen announced on October 22 that the conclusions from aducanumab's interim analysis for futility, disclosed on March 21, 2019, were incorrect.

In 2015, Biogen had initiated two large, identical phase 3 studies named EMERGE and ENGAGE, with over 1,600 participants having early Alzheimer's disease (AD) in each 78-week study. Based on data available by the December 2018 "cut-off", an interim analysis indicated the chance the two studies would successfully meet the primary endpoint in the final analysis was less than 20%. Biogen decided in March 2019 to halt the two studies for "futility" and disclose the results.

However, between December 2018 and March 2019, the study participants continued to be assessed according to the experimental protocol. Additional "on-drug" data were generated and analyzed during this timeframe, and even afterwards until the studies could be operationally brought to a complete halt.

Biogen then conducted a thorough analysis for efficacy and safety on the larger, final dataset. It is this dataset that supported the updated clinical interpretations shared in the Biogen announcement and their decision to file a marketing application with FDA early next year.

**The EMERGE study was unequivocally positive and great news for patients:** The larger EMERGE dataset showed a statistically significant reduction in cognitive and functional worsening amongst participants administered a high dose of aducanumab compared to placebo, but not the

lower dose. Imaging studies for amyloid and fluid-based biomarkers in cerebrospinal fluid also showed reductions at the high dose consistent with the clinical benefit.

Not only did these assessments show a consistent response to dose, they also showed a greater improvement over time. These data were also compatible with the more limited data generated by Biogen in their initial phase 1b study, first presented in March 2015.

The larger dataset supports the conclusion that aducanumab can modify the progression of AD. It does not halt disease progression or reverse it, but it does significantly slow down the disease progression and that it still hugely significant for the AD community.

The second study ENGAGE was not statistically significant on the clinical endpoints. Two protocol amendments apparently impacted the two studies in a differential fashion, and Biogen stated they will give a comprehensive presentation on these studies at a major scientific conference later this year. However, when a subset of ENGAGE study participants, who received the highest dose monthly for at least 10 months or greater, were analyzed, they too, like participants in the EMERGE study, showed a clinical benefit on the primary endpoint compared to the placebo group.

Therefore, it appears that the highest tested dose of aducanumab (10 mg per kilogram monthly) must be administered over a prolonged duration in order to observe a meaningful change in clinical outcome.

There should be no skepticism about this interpretation, or the conclusion that the EMERGE study was positive. Biogen has concluded that the positive EMERGE study results, supported by their phase 1b study results and the ENGAGE subset analysis, represents an approvable package of data for the FDA. They have met twice with FDA to review these analyses, and they plan to submit their marketing application early next year.

**We now have a substantial dataset to support the amyloid hypothesis of Alzheimer's disease:** Many analysts and some academic investigators were ready to "bury" the amyloid hypothesis after the aducanumab futility decision was announced. Other anti-amyloid antibodies had already failed in the clinic, and many had hoped that aducanumab would provide scientific support for the hypothesis that beta-amyloid aggregates are critical for the initiation and progression of the disease. But now, the pharmacologic and clinical activity observed in the large, updated aducanumab datasets indicate that years of research and development on an amyloid treatment approach, as well as thousands of papers on pertinent basic research, were justified and that the hypothesis is now a major step closer to validation.

**There is still significant need for an improved therapeutic with superior clinical benefit and safety compared to aducanumab:** The reported incidence of adverse ARIA-E (brain swelling) in

the larger dataset was 35% despite attempts with drug titration to minimize it. Clinical benefit is dependent upon the amount of the therapeutic antibody that reaches the pathogenic form of beta-amyloid (i.e., toxic oligomers). However, higher dosing with aducanumab cannot be achieved without an even higher risk of ARIA-E because of its off-target binding to plaque and vascular deposits of beta-amyloid.

Aducanumab is only weakly selective for the beta-amyloid toxic oligomer, but an antibody that selectively targets oligomers is anticipated to provide greater clinical benefit and safety. For example, PMN310, an antibody that strongly and selectively binds only toxic oligomers, has the tremendous potential of clinically impacting AD progression in a very beneficial manner without adverse, dose-limiting ARIA-E. Moreover, PMN310 is so selective that its full dose can focus entirely on neutralizing the toxic species of beta-amyloid.

In Biogen's press release, the CEO, Mr. Michel Vounatsos, noted these new data have an implication for other drugs having "similar approaches targeting amyloid beta". If aducanumab is ultimately approved by regulatory authorities, PMN310 will clearly have the potential to be "best in class" as a next generation therapeutic antibody.

**Recent advances in fluid-based biomarkers will enable earlier Go / No Go decision points as drug candidates move through clinical development:** When next-generation therapeutics become available for clinical testing, we will not have to wait until phase 3 to decide whether they provide real value to patients. The recent availability of blood- and CSF-based biomarkers to assess AD neuropathology and drug impact can now occur very early, and cost-effectively, during the development of a new therapeutic. For example, a clinical study as early as phase 1 with an open-label extension could potentially offer meaningful biomarker data, an inflection point in perceived value, and provide justification for increased scientific and financial investment in the next phase of clinical testing.