Biogen's early Alzheimer's data raise hopes, some eyebrows

Cambridge, Massachusetts–based Biogen's presentation in March of highly favorable interim data from PRIME, its phase 1b study of the antibody drug aducanumab, gave color to its announced decision three months earlier that it would move directly into phase 3 testing. It also revived hopes in the Alzheimer's disease community that a treatment based on targeting amyloid-beta (Aβ), a hallmark of Alzheimer's disease, is in hand. But opinion leaders have been quick to caution that the trial is not complete, there are gaps in the data that when filled could alter the view of its significance, and that in any event, PRIME was geared to establish safety and not clinical proof of efficacy.

Aducanumab is a human antibody that targets two types of accumulations of Aβ in the brain—fibrils and oligomers. In PRIME, a multiple ascending-dose study, Aβ levels measured by imaging decreased as aducanumab doses increased. The data, shown at the 12th International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders in Nice, France, are "the first convincing evidence I have seen that anything lowers brain amyloid in a measureable way on an imaging scan," says Rachelle Doody of the Baylor College of Medicine in Houston. PRIME is proof of the compound's ability to engage its target, she says—it gives a clinical signal of activity in a dose-related manner.

A change made during the clinical trial could temper that enthusiasm. Late last summer, Biogen added a middle-dose cohort (6 mg/kg) to the study and tabled plans to escalate to 30 mg/kg of drug—presumably because it had begun to see edema, especially at the higher dose (10 mg/kg) it had been testing, and notably in participants with the *APOE*4* allele, known to contribute to worsening disease. Nonetheless, in December, the company announced it would move directly into phase 3.

"Everything they did was reasonable," says Lon Schneider of the Keck School of Medicine of the University of Southern California in Los Angeles. The study was a complete success, he says—Biogen got its dose range, safety signal and pharmacodynamic effect on amyloid to allow the drug to advance.

But given the interim nature of the data, any claims of a clinical effect are a reach. In a press release, Biogen stated that this is the first investigational drug for Alzheimer's disease to demonstrate a statistically significant slowing of clinical impairment in patients with prodromal (early symptomatic) or mild disease. "They say the clinical outcomes are exploratory, but they overstate it," Schneider notes. At least 30 more patients on a 6-mg dose have to be assessed at 12 months, and 10 more placebo patients at 12 months—roughly one-quarter of the 166 patients reported in March. Depending on how they fare, the outcomes of those patients could greatly shift the perceived clinical significance of the findings.

The Alzheimer's disease community has seen similarly encouraging early data before. In the phase 1b study of the Aβ-targeting antibody bapineuzumab, a high-profile drug candidate from New York–based Pfizer's Wyeth unit, small groups of patients in the highest dose group showed what appeared to some to be a significant difference on the MMSE, a scale of dementia severity also used by Biogen in PRIME. That phase 1b study was also geared to monitor safety and the patient numbers were small. After a series of costly late-stage failures, Pfizer and its partners finally discontinued development of bapineuzumab in 2012.

The failure tarnished the entire Aβ treatment theory as bapineuzumab appeared to hit its target. But programs with anti-Aβ antibodies continued nonetheless. "We now have three studies that support amyloid as a target," says Doody. In addition to PRIME, there is a subgroup analysis of the effect of the phase 3 antibody solanezumab, from Eli Lilly in Indianapolis, in mildly affected patients and recently reported phase 2 data with crenezumab, which Basel-based Roche is developing. "None of these prove efficacy, none of it prioritizes amyloid as a treatment target, but it all supports amyloid as a treatment target," she says.

If aducanumab proves effective, it may be due to the discovery approach taken by Neurimmune, the Zurich-based company that licensed the molecule to Biogen in 2007. It found aducanumab by screening healthy elderly individuals who did not have Alzheimer's disease for antibodies that could be protective. This rationale is similar to that explored by Baxter InHealthcare with intravenous immunoglobulin in Alzheimer's disease. But Baxter, in Deerfield, Illinois, stopped development of the immunoglobulin after a phase 3 study failed to demonstrate efficacy.

Neurimmune found that aducanumab was effective against fibrils and oligomers (including decamers, which may be more toxic), so it could both break up plaque and clean up oligomers. Plus, it does not attach to soluble amyloid in the vasculature (unlike solanezumab, for example, which attacks soluble Aβ). Neurimmune has also identified antibodies against α-synuclein and tau protein, using the same method.

That antibodies are truly protective is "an interesting hypothesis that may be correct," says chief medical officer Alfred Sandrock. Antibodies themselves are large molecules that need to clear the blood-brain barrier. "When you only have 0.1–0.5% getting into the brain you need high potency and selectivity," he says, "because you know you are going to be using large quantities of antibody."

The company is confident that aducanumab is naturally potent and very specific, Sandrock says, in some measure because they did not have to perform any affinity maturation *in vitro*. The volunteers' own immune systems did that, he says, probably because they were constantly exposed to these antigens.

In addition to aducanumab, Biogen is developing Tokyo-based Eisai's BAN2401, an antibody against a different Aβ epitope. Aducanumab binds to fibrillary Aβ. The Eisai antibody, on the other hand, targets proto-fibrils. In addition to its partnering with Eisai on BAN2401 and BACE1 (β-secretase) inhibitor E2609, about to enter phase 2, Biogen is participating in the UK Dementia Discovery Fund (**Box 1**).

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Box 1 Industry backs UK Dementia Discovery Fund

A new venture capital fund focused on novel approaches to treat and prevent dementia has reached $100 million. In March, Britain's health secretary Jeremy Hunt announced that the money had been raised by bringing together leading drug makers with support from the British government. This investment vehicle seeks to accelerate research and bring new drug candidates to treat dementia to the clinical stage, at which time they would be licensed to companies for further development. Pharma partners, including Biogen; Johnson & Johnson Innovation in Cambridge, Massachusetts; GlaxoSmithKline in London; Eli Lilly; and Pfizer have joined Alzheimer's Research UK charity in Cambridge and the UK government in the effort. The UK government kicked off the fund last autumn with $22.2 million, GlaxoSmithKline added $25 million and Johnson & Johnson put up $10 million; other companies also contributed. JP Morgan in New York is providing guidance to structure the fund and help identify additional private sector support.