Will the FDA Advisory Committee on November 6th recommend approval of Biogen's aducanumab application? A ProMIS "reading of the tea leaves"

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- **Biogen announced July 8, 2020, it had completed the FDA submission of its Biologics License Application (BLA) for aducanumab, and then announced on August 7, 2020, that FDA had accepted the application, granted it Priority Review, and set the Prescription Drug User Fee Act target date for March 7, 2021**
- **Less than 8 weeks later, FDA announced it would convene an Advisory Committee (AC) of scientific experts on November 6, 2020, to provide "advice and recommendations" on the aducanumab BLA as this drug would represent the first disease-modifying therapy for Alzheimer's disease if approved**
- **The AC will debate whether the data contained within the BLA justify Biogen's claim that the drug provides "substantial evidence of effectiveness" and that it is adequately safe. The AC provides recommendations, but the final decision will be made by FDA.**
- **The phase 3 EMERGE trial was unequivocally positive, and it is our view that the majority of AC members will conclude that subset data from the phase 3 ENGAGE trial and the overall phase 1b PRIME trial results provide the requisite confirmatory evidence**
- **FDA has encouraged Biogen to submit this BLA, endorsed continued clinical use of aducanumab in an open-label study, and shown its willingness to approve drugs despite limited data in instances where there is a significant unmet medical need**
- **Although we conclude aducanumab is likely to be approved by FDA, its modest efficacy and safety concerns justify the need for a next-generation therapeutic that selectively targets toxic oligomers, offering the potential for improved safety and efficacy**

It has been a very busy year for the aducanumab project team at Biogen, and their efforts will culminate on November 6th when they publicly defend the aducanumab Biologics License Application (BLA) for the treatment of Alzheimer's disease (AD) before the Peripheral and Central Nervous System Drugs Advisory Committee (AC).

Despite the direct impact of COVID-19 on members of the Biogen team, they completed their "rolling BLA" submission in early July after meeting with FDA for their planned "pre-BLA meeting" to ensure all application components were complete. Although FDA then had up to 60 days to decide whether to accept the application for review, Biogen announced just 30 days after their submission that FDA had accepted the application. Moreover, FDA opted to grant the application priority review, setting a Prescription Drug User Fee Act (PDUFA) target action date for March 7, 2021, and thereby committing to a significantly reduced review period.

Biogen also revealed that FDA granted the BLA priority review without Biogen needing to submit a Priority Review Voucher (which they had apparently received from FDA in December 2016, in response to its successful Spinraza application for the treatment of spinal muscular atrophy, a pediatric rare disease). A non-voucher priority review strongly suggests that the FDA believes aducanumab potentially represents a major advance for the treatment of AD. Biogen also indicated the FDA *"has stated that, if possible, it plans to act early on this application,"* also suggesting FDA is already well-informed regarding the application data and is seriously contemplating approval.

In light of the PDUFA target date next March, most of us in this area of research anticipated FDA would schedule an AC meeting early next year. However, FDA surprised everyone by publishing in the Federal Register on September 29th that the AC would be convened on Friday, November 6th. Such a rapid announcement less than two months after accepting the application suggests that FDA has already reached internal consensus on whether they view the application as approvable.

Why convene an Advisory Committee meeting, and how will it be conducted?

The FDA Office of Neuroscience, consisting of five review divisions, does not often convene the Peripheral and Central Nervous System Drugs Advisory Committee. For example, the Office of Neuroscience approved in 2018 and 2019 some 18 new novel drugs, yet convened only one AC meeting to solicit recommendations from external experts. The large majority of drug applications are relatively straightforward and the agency can efficiently decide whether to accept or reject the application.

In situations in which there are significant questions about the clinical evidence and conclusions contained in the application, or in which there is strong public interest due to the disease or the novelty of the therapeutic approach, the Office of Neuroscience (Billy Dunn, MD, Director) can decide to convene an AC to solicit advice and recommendations. The AC membership is currently composed of nine voting academic experts in neurology, psychiatry, biostatistics, epidemiology and internal medicine, as well as one consumer representative. In addition, one non-voting member from industry who is an expert in neuroscience drug development also currently serves on the AC.

The 6-hour AC meeting for aducanumab will be virtually convened due to COVID-19 restrictions and streamed via the internet. After introductions and short FDA opening remarks, I expect Biogen will have one hour to highlight the key components of their application and make their case for aducanumab's approval. The FDA team, typically led by the medical reviewers, will then, over the next hour, provide their analysis of aducanumab's benefit/risk assessment and their perspective on the approvability of the application (note: the FDA slide pack which provides their analysis is often posted a few days before the AC meeting). Clarifying questions at the end of each presentation are allowed. At the end of the FDA presentation, FDA will provide a list of questions they wish the AC to vote on at the conclusion of the meeting (although these questions could be offered up at the beginning of the meeting during FDA opening remarks).

After a lunch break, I expect there will be a one-hour open public hearing where various interested parties (non-Biogen, non-FDA) will comment on the application. As this is the first application for a disease-modifying therapy targeting AD, I suspect there will be families, with a member having AD,

who will argue for approval as AD is a significant unmet medical need and there is currently no available therapy that provides any hope of reducing the progression of the disease. I also suspect that patients who have participated in the aducanumab clinical studies may independently provide their perspective of the drug's benefit. The high level of expressed emotionality I expect during the public hearing may or may not impact the final decision-making by AC members, but it will linger in the background as AC members debate the questions.

The Chairperson may or may not initially go around the table asking committee members for their preliminary thoughts. The AC then engages in debate, and the pros and cons of supporting a yes or no vote on each FDA question will be deliberated by the AC. Once the Chairperson concludes all outstanding issues have been surfaced and adequately addressed, he will call for a vote on each question and then adjourn the meeting.

What issues will the AC debate? The FDA will likely pose a series of questions to the AC regarding the BLA's demonstration of adequate effectiveness and acceptable safety to substantiate FDA approval of the BLA for the purposes of marketing aducanumab. I also suspect FDA may question the AC on the generalizability of aducanumab's use in AD.

(1) Substantial Evidence of Effectiveness: The most significant FDA concern is whether the external experts conclude the BLA has demonstrated "substantial evidence of effectiveness". This licensing requirement has generally been interpreted as calling for two adequate and well-controlled clinical trials that are positive. However, under certain circumstances and consistent with the 1997 FDA Modernization Act, FDA can conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness.

In the aducanumab BLA, clinical data from two large Phase 3 studies (EMERGE, ENGAGE) and one Phase 1b study (PRIME) comprise the dataset supporting approval.

Only the EMERGE trial was unequivocally positive based upon an analysis of the final dataset. The analysis showed a statistically significant 23% reduction in cognitive decline on the primary endpoint (Clinical Dementia Rating–Sum of Boxes [CDR-SB] at the highest dose of 10 mg/kg). All secondary cognitive and functional endpoints were also statistically significant and Biogen's biomarker analyses support the interpretation that aducanumab beneficially impacts the underlying AD neuropathology.

The ENGAGE trial did not show an overall treatment benefit like EMERGE because of the discordant impact of a 2017 protocol amendment on these two trials that differentially increased the percentage of subjects in the EMERGE trial who received the maximum dose of 10 mg/kg for a prolonged period of time. Despite the negative outcome on the primary and secondary endpoints in the ENGAGE study, a *post-hoc* analysis showed that the subset of ENGAGE participants (n=790) who had consented to the high-dose protocol amendment early in their trial participation had a treatment benefit (-27%) on CDR-SB similar to that observed in the equivalent subset (n=887) of the EMERGE study (-30%).

Biogen concluded that trial subjects who demonstrated a reduction in their rate of clinical decline had consistently been administered the highest possible dose of aducanumab over a prolonged duration, and I agree with their conclusion. There are various statistical issues and subset analyses one must grapple with before accepting Biogen's position, and the AC will undoubtedly debate them.

With respect to BLA approvability, the dose-responsive impact of aducanumab on clinical endpoints and biomarkers in the smaller PRIME study also provides, in addition to the ENGAGE subset data noted above, the supporting evidence that confirms the effectiveness of aducanumab which was sufficiently demonstrated in the EMERGE study. The major question put before the AC will undoubtedly be whether the members agree with this position. The AC will acknowledge that aducanumab's treatment benefit is modest. However, they will also agree that the treatment benefit is clinically meaningful in the absence of any existing disease-modifying therapy for AD. They will wrestle with the question as to whether, in light of existing data, it is ethical and practicable for Biogen to conduct yet another large-scale, multi-year clinical investigation at the highest dose before reconsidering the BLA.

I predict a majority of the AC members will vote YES to the question as to whether the aducanumab BLA demonstrates substantial evidence of effectiveness, but there may be several strong dissents.

(2) Demonstration of adequate safety:

Carriers of the apoE4 gene have a higher risk of Amyloid-Related Imaging Abnormalities–Edema (ARIA-E; *i.e.*, patchy vasogenic brain edema) when administered anti-amyloid antibodies that bind amyloid plaque and dense deposits of amyloid in the brain vasculature. In fact, this is why Biogen scientists initially limited the maximum available dose administered to these apoE4 carriers in the EMERGE and ENGAGE studies, which were subsequently amended to rectify this restriction. At the highest dose, the overall incidence of ARIA-E is 35%, and this unpredictable side effect limits the maximum dose of aducanumab that can be administered to a group of AD patients.

This incidence of ARIA-E associated with aducanumab administration represents the highest rate associated with any anti-amyloid antibody tested to date in clinical studies, and the AC will be asked whether the use of aducanumab, if approved, should be restricted or managed to minimize the safety risk associated with its use. For example, I'm sure the AC will discuss the following questions regarding clinical management:

- Who can prescribe aducanumab? Should prescribing be limited to only AD specialists such as neurologists?
- How often (and when) should MRI scans of the brain be performed to assess for the presence of ARIA-E?
- Must a radiologist have specialized training in neuroradiology to assess the presence or absence of ARIA-E?
- Should a patient be titrated up to the maximum dose of aducanumab in an attempt to diminish the emergence of ARIA-E?
- Can a patient who developed ARIA-E ever be dosed again with aducanumab?

(3) Restrictions on who should receive the drug

The phase 3 studies were conducted in subjects with early AD. Early AD is comprised of symptomatic patients with mild cognitive impairment or mild dementia due to AD. In the phase 3 studies, subjects had to have demonstrated brain amyloid for trial consideration as a means to confirm they had the critical neuropathologic change consistent with a diagnosis of AD. Typically, such change is shown by either specialized PET imaging or drawing CSF via lumbar puncture to enable a specialized lab analysis for abnormal amyloid. More severe patients having moderate dementia or, at the other extreme, asymptomatic patients at risk of AD and having evidence of AD neuropathology were not evaluated in the aducanumab clinical studies. If the AC votes YES for approval, they will be asked to confirm that aducanumab should only be prescribed for patients with early AD. Administration of aducanumab to others would represent "off-label" use.

Final Comments: AD is one of the highest unmet medical need indications in medicine and FDA is committed to approving a drug for this indication. FDA neuroscientists and team leaders have been active in promoting the development of new cognitive endpoints and biomarkers to demonstrate drug impact on the underlying neurobiology of AD.

The FDA has already demonstrated its sensitivity to medical need in the past. For example, when edaravone was approved in Japan in 2015 for the treatment of ALS on the basis of a single 6-month study evaluating 137 subjects, FDA strongly encouraged Mitsubishi Tanabe Pharma to file a marketing application in the US; the drug was quickly approved and FDA required post-approval commitments by Mitsubishi. A similar example occurred in 2019 when FDA granted accelerated approval for golodirsen for the treatment of Duchenne muscular dystrophy based on a very limited clinical dataset, requiring the sponsor (Serepta) to conduct a clinical trial to confirm the drug's clinical benefit.

FDA's potential approval of aducanumab, despite its modest treatment benefit, will encourage other sponsors to develop next-generation therapies that have greater efficacy and better safety. ProMIS is developing an anti-amyloid antibody (PMN310) that selectively binds the toxic oligomer of amyloid-beta (not plaque or monomers), and we therefore expect PMN310 will demonstrate much greater efficacy without the side effect of ARIA-E.

FDA leadership and scientists have met on multiple occasions with Biogen over the last year, and FDA has shown a deep interest in encouraging Biogen to prepare the BLA for submission. Moreover, FDA endorsed continued clinical use of the drug by approving the resumption of aducanumab testing in an open-label study to collect additional safety data.

The FDA thus appears to be willing to approve the aducanumab BLA, but needs the AC members to confirm and validate its assessment. A positive recommendation at the November 6th Advisory Committee meeting will both provide support to FDA in its decision making and catalyze investor interest in the next generation of therapies targeting amyloid.