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POLICY FORUM

Open Peer Commentary to "Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE Trials as reported by Biogen December 2019"

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By full disclosure, MNS advises Biogen's aducanumab, Eisai's BAN2401 program, Roche's Gantanerumab, Alzheon's Alz801 program, Cortexyme COR388 program, and Athira's NDX1017. In the past, MNS was on the steering committee of the Pfizer/Wyeth Bapineuzemab program and advised Lilly's solanazumab and Axovant's Interpredine program and VTV therapeutics Azeliragon program. This disclosure is intended for transparency and to give the reader the perspective of no exclusionary bias toward or against aducanumab.

Dr. Cummings has provided consultation to Acadia, Actinogen, Acumen, Alector, Alkahest, Alzheon, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Cassava, Cerecin, Cerevel, Cortexyme, Cytox, EIP Pharma, Eisai, Foresight, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, Merck, Novo Nordisk, Otsuka, ReMYND, Resverlogix, Roche, Samumed, Samus, Signant Health, Sunovion, Suven, and United Neuroscience pharmaceutical and assessment companies.

A US Food and Drug Administration (FDA) Advisory Committee will soon review data submitted by Biogen for approval of aducanumab for the slowing progression of Alzheimer's disease (AD). If approved, aducanumab will be the first of treatment for AD approved in the US since 2003, the first treatment for mild cognitive impairment due to AD, the first approved agent to target the amyloid protein, and the first drug with a putative disease-modifying mechanism for the treatment of AD. In this issue of *Alzheimer's & Dementia*, Dr. Knopman and colleagues[1] challenge the efficacy data of aducanumab. In view of the importance of this decision, we offer additional perspectives for consideration. Both authors have consulted for Biogen, the comments presented are our own and were not requested by or reviewed with Biogen. The results of the aducanumab studies have not been published in peer-reviewed form and both the analysis presented by Dr Knopman and collaborators and this perspective are based on data presented in 2019 at the Clinical Trials in AD (CTAD) meeting[3]; both discussions must be seen as tentative until full data are available.

Aducanumab is a human monoclonal antibody targeting aggregated amyloid including neuritic amyloid plaques and high molecular weight amyloid oligomers (ABO).[2] It enters the brain at low concentrations, binds to amyloid plaques and ABO, stimulating microglia to clear the amyloid species. Aducanumab has consistently shown substantial, dose- and treatment duration-related lowering of amyloid plaques across the Phase 1b (PRIME trial)[4] and Phase 3 studies.[3] Target engagement by aducanumab is well supported by these studies.

Analysis of the Phase 3 EMERGE and ENGAGE studies is complex; both studies were declared futile on the basis of pre-specified futility thresholds.[3] In view of the urgent need for therapies of AD, our goal in considering the outcome is to determine if efficacy occurred and was compelling beyond the strict limits of the futility analyses. Futility analyses occurred when 50% of the patient had the completed 78 weeks of therapy. When the complete patient data are included in the analysis, the EMERGE study met its primary endpoint of slowing of cognitive decline on the Clinical Dementia Rating-Sum of Boxes (CDR-SB). This outcome was supported by slowing of decline on secondary

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cognitive and functional measures in EMERGE and positive findings on the CDR-SB in the highest dose arm of the PRIME trial. The ENGAGE trial is more complex and did not demonstrate a drug-placebo difference on the CDR-SB in the larger data set. Although ENGAGE and EMERGE had identical protocols they began at different times and fewer patients in ENGAGE had enduring treatment (14 doses) of the high dose (10 mg/kg) than EMERGE. When patients in ENGAGE receiving the same exposure of those in EMERGE were analyzed, they had similar treatment outcomes on the CDR-SB suggesting that the total exposure was critical and sufficient to explain the treatment effect.

EMERGE and ENGAGE included substudies of cerebrospinal fluid (CSF) biomarkers. Although the number of patients included in the substudies is small, there was a dose-related decrease of CSF phosphorylated tau (p-tau) and a nonsignificant trend toward diminished total tau.[3] In addition, there was as significant decrease in temporal, medial temporal, and frontal composites of standard uptake value ratios (SUVR) on tau positron emission tomography (PET). Significant dose and time-related reductions in amyloid PET SUVR were demonstrated in EMERGE and ENGAGE. The observations suggest that engaging and removing insoluble amyloid plaques and ABO is followed by "downstream" effects on markers of p-tau and tau PET associated with neurofibrillary tangles. The biomarkers support a disease-modifying effect of aducanumab.

ARIA was the most common side-effect of aducanumab; this was primarily transient and manageable using a titration schedule and safety monitoring with MRI.

Previous mABs that include bapinuezemab,[5] solanezumab,[6] and crenazumab have not met primary efficacy endpoints in symptomatic AD trials. Aducanumab is the first mAB to show directional concordance of removal of amyloid and slowing of cognitive decline. Previous mABs either showed a clinical efficacy signal (EXPEDITION 1) or removal of amyloid[7] but not both. The effect of aducanumab appears to be dose- and treatment-duration dependent. Clinical effects might be secondary to other actions beyond amyloid removal (reduced tau, reduced inflammation, making the milieu healthier, etc).

We stand at a crucial transition point in the diagnosis and treatment of AD. When human immunodeficiency virus (HIV) infection was first identified there was no approved treatment. Azidothymidine (AZT) had limitations but approval of energized the HIV and scientific community and through advocacy and intensive research combination treatments were developed that substantially reduce morbidity and improve longevity and quality of life. Similarly, lovastatin was the first β-Hydroxy β-methylglutaryl-CoA (HMG CoA) reductase inhibitor approved; it produced a significant mean reduction in LDL cholesterol, had few adverse effects, and was easy for patients to take. Lovastatin was rapidly followed by simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin and rosuvastatin.[8] In AD therapeutics, tacrine was the first approved treatment and was soon followed by approval of donepezil, rivastigmine and galantamine with enhanced tolerability and safety and improved pharmacokinetics.

Approval of aducanumab would represent the beginning of the modern treatment era for AD similarly stimulating the field as was seen with statins and HIV treatments. This is not a cure but the first incremental step in transforming the disease from an untreatable terminal illness to a manageable chronic disease. Advancing aducanumab forward toward approval could pave the way for other monoclonal antibodies and therapeutic interventions.

Lack of approval would be devastating not only to patients who will lose hope but advocates and the community at large. It would deny access to the positive benefits of this treatment for 4-5 years resulting in devastating disease progression and burden of care for patients and families. It will have a chilling effect on investment in AD research and development. We believe the data are sufficient to warrant approval with Phase 4 surveillance. This stance is endorsed by the Alzheimer's Association per their website statement. All factors need to be considered as the FDA renders their decision.

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