Testimony Before the FDA's Peripheral and Central Nervous System Drugs Advisory Committee: The FDA Must Reject BLA 761178 for Aducanumab for the Treatment of Alzheimer's Disease

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I have no financial conflicts of interest.

Introduction

Public Citizen strongly opposes FDA approval of aducanumab for the treatment of Alzheimer's disease because the pivotal phase 3 trials ENGAGE (study 301) and EMERGE (study 302), plus the phase 1 study 103, fail to provide substantial evidence of efficacy.

Lack of Substantial Evidence of Efficacy

The pivotal trials were terminated early after the prespecified interim analysis for futility showed that only EMERGE was trending positive whereas ENGAGE was unlikely to meet its primary endpoints.

A subsequent post hoc analysis of the trials showed that in EMERGE high-dose aducanumab provided a statistically significant but small improvement in the primary efficacy endpoint but in ENGAGE no benefit with low- or high-dose aducanumab. Such post hoc analyses are highly susceptible to bias, do not provide substantial evidence of efficacy, and should only be used to generate hypotheses for possible future trials.

Lack of Substantial Evidence of Efficacy (cont.)

Dr. David Knopman, a Mayo Clinic neurologist and member of this Committee who is recused today because he was a site investigator for ENGAGE:

> **"[T]he evidence that aducanumab…has any benefits in persons with [Alzheimer's disease] is *terribly weak*… [Emphasis added]**

Statement by Dr. David Knopman, M.D., https://beta.regulations.gov/comment/FDA-2018-N-0410-0034

Failed Drugs Targeting Amyloid-β (Aβ) Accumulation

Drug Class	Drug name (publication year of final phase trial(s); last trial phase conducted; reason(s) for failure)
Aβ antigens	• AN-1792 (2002; phase 2; toxicity and lack of efficacy) • Vanutide (2013; phase 2; lack of efficacy) • Affitope AD02 (2014; phase 2; lack of efficacy, worsened cognition) • CAD106 (2014; phase 2; lack of efficacy, worsened cognition)
Aβ aggregation inhibitors	• Tramiprosate (2007; phase 3; lack of efficacy) • Scyllo-inositol (2009; phase 2; toxicity and lack of efficacy, increased mortality) • PBT2 (2014; phase 2; lack of efficacy)
γ-Secretase modulator	• Tarenflurbil (2009; phase 3; lack of efficacy, worsened global status)
γ-Secretase inhibitors	• Begacestat (2010; phase 2; toxicity and lack of efficacy) • Semagacestat (2011; phase 3; toxicity and lack of efficacy, worsened cognition) • Avagacestat (2012; phase 2 (2 trials); toxicity and lack of efficacy, worsened cognition)
Anti-Aβ monoclonal antibodies	• Ponezumab (2011; phase 2; lack of efficacy) • Bapineuzumab (2012; phase 3; lack of efficacy) • Crenezumab (2014; phase 2; lack of efficacy) • Gantenerumab (2014; phase 2 (2 trials); lack of efficacy) • Solanezumab (2013 (1 trial), 2016 (2 trials); phase 3 (3 trials); lack of efficacy)
Anti- Aβ polyclonal antibody	• Immunoglobulin (2013; phase 3; lack of efficacy)
β-secretase inhibitor	• LY2886721 (2013; phase 2; toxicity) • AZD3839 (2013; phase 1; toxicity) • Verubecestat (2016 (1 trial), 2018 (1 trial); phase 3 (2 trials); lack of efficacy, increased mortality, worsened cognition) • Atabecestat (2018; phase 3; toxicity, worsened cognition) • Lanabecestat (2018; phase 3 (2 trials); lack of efficacy, worsened cognition)

Panza et al. *Nat Rev Neurol*. 2019;15(2):73-88.

FDA Statistical Reviewer's Assessment

FDA statistical reviewer Tristan Massie, Ph.D., correctly highlighted the lack of substantial evidence of efficacy for aducanumab, noting that:

> **"In this case we do not have a single strong study in isolation. On the contrary, we actually have a second trial in which the purported effective dose was in the wrong direction compared to placebo, i.e., numerically worse than placebo. Under the null, if winning in just one study out of two was enough, then the chance of falsely rejecting the null would be .0975 across the two studies. Furthermore, if we select only the better study, our estimate is very likely biased, and we already know not consistently repeatable in our experience. *Thus, excluding data from a large trial without sufficient justification is unscientific, statistically inappropriate and misleading*." [Emphasis added]**

https://www.fda.gov/media/143505/download, PDF p. 25

Conclusions

In closing, the FDA must demand another large premarket randomized, placebo-controlled trial of aducanumab. FDA approval of the drug, absent substantial evidence of efficacy, would further damage the agency's already diminished credibility.

We therefore urge the committee to vote "No" on question 7 and recommend that the FDA not approve aducanumab.