

## The mechanism of action of the controversial drug; aducanumab and the story behind its speedy approval

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Madam, Alzheimer's disease is a neurodegenerative disease and is denoted by memory loss and cognitive deterioration. It gives rise to the two pathologic hallmarks: the neurofibrillary tangles and amyloid plaques.<sup>1,2</sup>

Aducanumab is a monoclonal human immunoglobulin gamma 1 (IgG1) antibody that targets the amyloid plaques. The mechanism of action comes into play when this antibody crosses the blood-brain barrier and binds to aggregates of A $\beta$  amyloid plaques composed of neurotoxic soluble oligomers and insoluble fibrils structures. Aducanumab has a strong affinity with amyloid aggregates. It can discriminate between A $\beta$  monomers and fibrillar or oligomeric aggregates. Aducanumab selectively targets the aggregates of A $\beta$  plaques which are formed extracellularly in the brain.<sup>3</sup>

After the success of the phase 1B trial, Biogen, the sponsor of the aducanumab trial, started two phase 3 trials known as EMERGE and ENGAGE. After adding accumulated blinded data, it was revealed that EMERGE trial has successfully met its primary outcome but ENGAGE failed to do so. Biogen submitted the results to the US Food and Drug Administration (FDA) for review. An FDA advisory committee opposed the approval of aducanumab based on a single study that showed promising results.

FDA concluded that there were "residual uncertainties regarding clinical benefit" and the drug "may provide meaningful therapeutic benefit" based on a surrogate endpoint "that is reasonably likely to predict a clinical benefit." The surrogate was amyloid reduction, and the clinical benefit was slowing of cognitive impairment.

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**DOI:** <https://doi.org/10.47391/JPMA.5049>

Aducanumab was given license under the pathway of "accelerated approval". For further reassurance, Biogen agreed to conduct a nine-year post-approval confirmatory study. Phase four trials are being conducted to identify rare side effects and the real-world effectiveness of the drug. These trials do not have the ability to demonstrate efficacy. Whether aducanumab slows cognitive decline will only be known until at least in 2030, using this period, the drug will cost 56000 USD (9,494,800 PKR) per person annually.

Supporters of FDA approval argue that EMERGE trial met its primary outcome. In contrast, ENGAGE participants saw benefits after being treated with a high dose for a longer duration. They believe this evidence is sufficient to establish the therapeutic benefit of this drug. On the other hand, the opposers believe that history is repeating itself. In 2018, dementia drugs i.e., donepezil, galantamine, etc. were defunded in France because no clinical benefit was observed after a decade of their use.<sup>4,5</sup>

**Acknowledgement:** None.

**Disclaimer:** None.

**Conflict of Interest:** None.

**Funding Disclosure:** None.

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