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Lecanemab – Updated clinical data indicate a modest clinical effect on the disease, with a moderate rate of serious adverse events.

Key highlights

- Lecanemab, a monoclonal antibody, clears amyloid and being studied to determine ability to slow the progression of cognitive decline.
- While study results demonstrated statistically significant slower decline in cognitive function vs placebo, it is unclear if 0.45 points on an 18-point scale represents a meaningful clinical change.
- Serious adverse events occurred in 14% of individuals receiving lecanemab vs. 11.3% with placebo.

Summary:

- On November 29, 2022, results from the lecanemab phase 3 pivotal trial, CLARITY-AD, were presented at the Clinical Trials in Alzheimer's Disease (CTAD) Congress in San Francisco, CA. Simultaneously, the trial findings were published in the *New England Journal of Medicine*. These results were highly anticipated. However, the data indicate a modest effect on the disease, with a moderate rate of serious adverse events. Unclear if effect correlates with clinically meaningful change
- Lecanemab, by Eisai/Biogen is currently being reviewed by FDA for the treatment of mild Alzheimer's disease. Lecanemab is a monoclonal antibody with a similar mechanism to Eisai/Biogen's Aduhelm® (aducanumab), which was approved in June 2021 with much controversy due to unclear efficacy and known toxicity. The Centers for Medicare and Medicaid Services (CMS) ultimately decided to only cover Aduhelm if it were used in a CMS approved clinical trial, effectively severely limiting uptake of Aduhelm (commercial sales of $3M in 2022 worldwide). This approach could also apply to lecanemab if it receives accelerated approval from the FDA, as expected. Forecasted price for lecanemab is $28,200 per year (based on Aduhelm's WAC price).
- **Overview of CLARITY-AD trial**
  - The trial studied 1,795 individuals 50 to 90 years old with early Alzheimer's disease
  - Individuals received either intravenous (IV) lecanemab 10 mg per kg or IV placebo every 2 weeks for 18 months
  - Lecanemab was associated with a statistically slower decline in cognitive function; a -0.45 point difference vs. placebo on the 18-point Clinical Dementia Rating-Sum of Boxes (CDR-SB) scale. While statistically significant, it is unclear if 0.45 points on an 18-point scale represents a meaningful clinical change.
    - The CDR-SB scale is a standardized and validated scale used to assess cognitive and functional domains of Alzheimer's disease disability.
  - Serious adverse events occurred in 14% of individuals receiving lecanemab vs. 11.3% with placebo.
  - Amyloid related imaging abnormalities (ARIA), a known toxicity of this class of drugs, were closely monitored throughout the trial
    - ARIA with edema (ARIA-E) occurred in 12.6% with lecanemab vs. 1.7% with placebo

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- ARIA with hemorrhage (ARIA-H) occurred in 17.3% with lecanemab vs. 9% with placebo
- Individuals with the *ApoE-ε4* genetic biomarker had higher rates of ARIA-E and ARIA-H relative to individuals without the biomarker.

What is next?

- **Accelerated Approval:** Lecanemab is seeking accelerated approval for treatment of mild Alzheimer's disease based on data indicating lecanemab lowers brain beta amyloid in a phase 2 trial. The phase 3, CLARITY-AD trial also indicated lecanemab significantly lowered brain beta amyloid relative to placebo, but it is not clear that reducing beta amyloid translates to meaningful clinical improvement. An FDA approval decision is expected by January 6, 2023.
    - Eisai/Biogen are expected to file for full FDA approval in 2023. Full FDA approval could prompt CMS to revise their current policy that prevents coverage of anti-amyloid antibodies for Alzheimer's disease unless they are enrolled in a clinical trial.
- **Amyloid Hypothesis:** Brain amyloid proteins as the source of Alzheimer's disease is a topic of considerable scientific debate. Some believe other disease processes or and proteins are more likely to be the cause of Alzheimer's disease. The findings from the CLARITY-AD trial do not resolve this debate.

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