Efficacy of Lecanemab in Patients With Early Alzheimer's Disease: A Systematic Review and Meta-Analysis

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Conclusion

Lecanemab demonstrated a decrease in cognitive and functional decline compared to placebo for the treatment of early-stage AD over 18-months period. Future meta-analysis studies should also include the safety and tolerability outcomes. Further, longer-term studies are needed to evaluate the effectiveness and safety of lecanemab for the treatment of early-stage AD

Background

- Alzheimer's disease (AD) is a progressive neurodegenerative condition that primarily affects the cerebral cortex and hippocampus region of the brain. It typically begins in the frontal and temporal lobes and gradually spreads to the other regions at varying rates among individuals[1]
- AD is characterized by the accumulation of beta-amyloid (Aβ) protein in the brain's extracellular spaces and blood vessel walls, as well as the aggregation of tau protein into neurofibrillary tangles within the neurons[1]
- The treatment options specifically designed to address Aβ-pathology have recently been available, which aim to significantly diminish the accumulation of aggregated Aβ plaques, lower the levels of soluble Aβ, and decrease the production of Aβ species prone to aggregation[2, 3]
- Lecanemab is a humanized monoclonal antibody which binds to soluble Aβ protofibrils with high affinity to treat early AD[4]

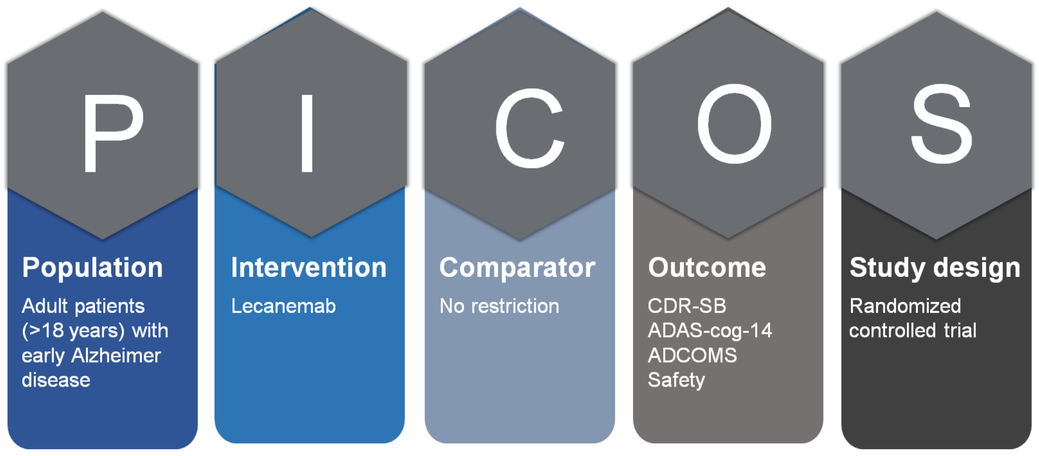
Objective

- The objective of this meta-analysis is to review the clinical evidence for lecanemab in patients with early AD

Methodology

- This review adhered to NICE and PRISMA guidelines for systematic literature reviews (SLRs), following standard methodology with transparent, reproducible, and unbiased approach
- A systematic search of published literature was performed using Embase® and MEDLINE® from database inception to June 2023 to identify the randomized controlled trials assessing lecanemab in early AD
- Two independent reviewers performed the screening and data extraction activities, with conflicts resolved by a third independent reviewer
- **Figure 1** presents the pre-defined PICOS criteria for study selection

Figure 1: Prespecified PICOS eligibility criteria for selection of evidence



ADAS-cog-14: Alzheimer's Disease Assessment Scale-Cognitive Subscale ; ADCOMS: Alzheimer's Disease Composite Score; CDR-SB: Clinical Dementia Rating-Sum-of-Boxes ;

- The outcomes of interest included change from baseline in Clinical Dementia Rating-Sum-of-Boxes (CDR-SB), Alzheimer's Disease Composite Score (ADCOMS), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14) at 18 months
- The meta-analysis was performed using Stata 17 software

Results

- Two double-blind, placebo-controlled, 18-months trials (Study 201, and Clarity AD) met the inclusion criteria
- The flow of publications through the entire SLR process is depicted in the PRISMA diagram **(Figure 2)**
- **Methodological characteristics:** Both the trials were similar in blinding, geography, and the reported outcome types whereas differ in trial phase. Study 201 and Clarity trial was conducted in phase II and III setting, respectively **(Table 1)**
- **Clinical characteristics:** While the majority of clinical characteristics were similar between both trials, the Clarity trial reported a higher proportion of females and cases of mild dementia due to AD. In contrast, Study 201 exhibited a larger number of patients with mild cognitive impairment due to AD and a global Clinical Dementia Rating (CDR) score of 0.5 **(Figure 3)**

Results (Cont'd)

Figure 2: PRISMA diagram for the screening process

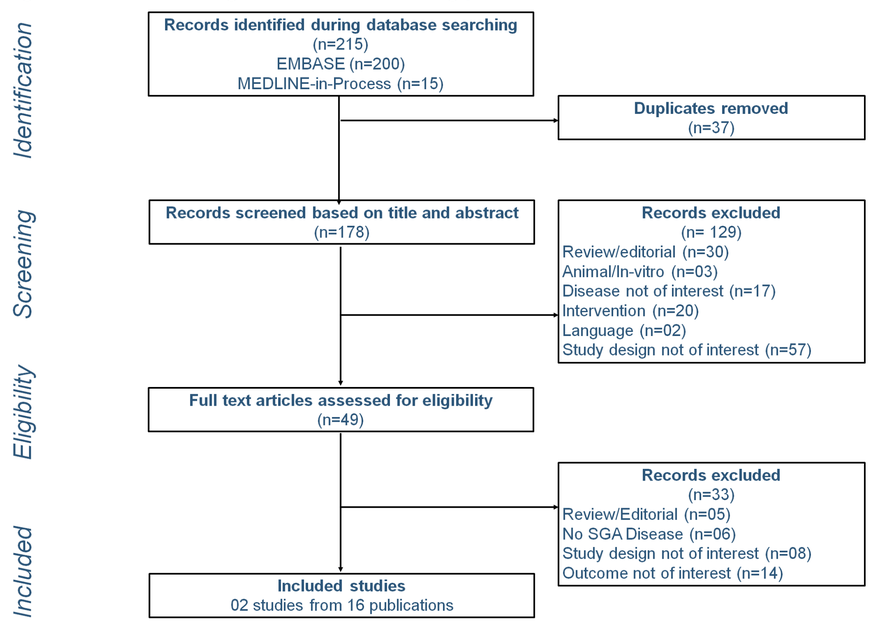
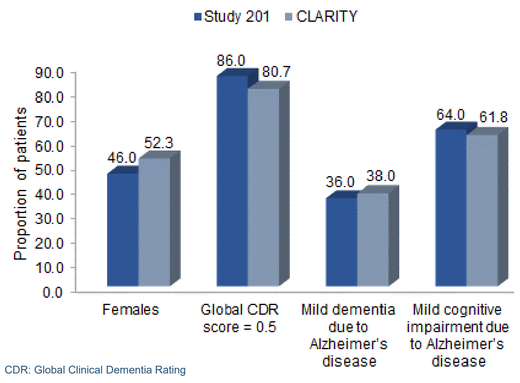


Table 1: Characteristics of included RCTs

Parameters	Clarity	Study 201
Phase-III	✓	✗
Blinding (Double Blind)	✓	✓
Global (Multiple countries)	✓	✓
CDR-SB	✓	✓
ADAS-cog-14	✓	✓
ADCOMS	✓	✓
Safety	✓	✓

CDR-SB: CDR–Sum of Boxes; ADAS-cog14:14-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCOMS: Alzheimer's Disease Composite Score

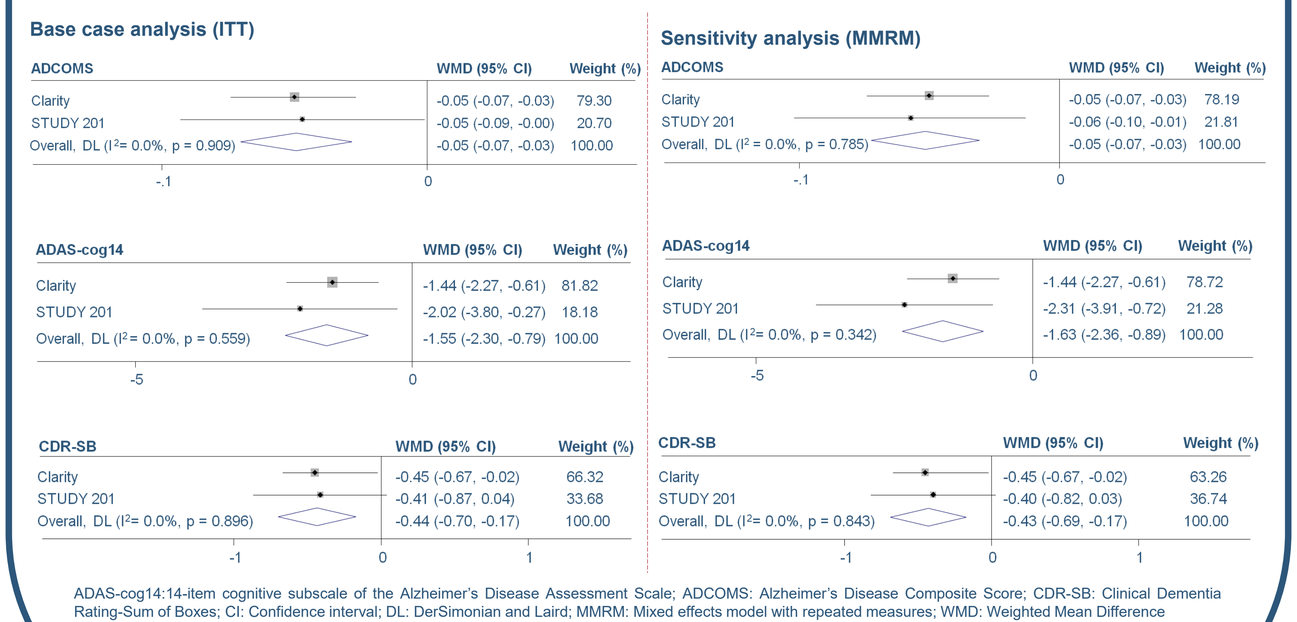
Figure 3: Clinical characteristics of patients across the included studies



CDR: Global Clinical Dementia Rating

- In the ITT analysis, lecanemab 10 mg biweekly was associated with statistically significantly better efficacy vs. placebo in terms of reduction on various scales: CDR-SB (WMD: -0.44, 95%CI: -0.70 to -0.17), ADCOMS (WMD: -0.05, 95%CI: -0.07 to -0.03), and ADAS-Cog14 (WMD: -1.55, 95%CI: -2.30 to -0.79) **(Figure 4)**
- A sensitivity analysis performed using MMRM, analysis, showed similar results (Figure 4)

Figure 4: Forest plot of meta-analysis of ADCOMS, ADAS-Cog14, and CDR-SB comparing lecanemab vs. placebo at 18 months



ADAS-cog14:14-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCOMS: Alzheimer's Disease Composite Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: Confidence interval; DL: DerSimonian and Laird; MMRM: Mixed effects model with repeated measures; WMD: Weighted Mean Difference

Thresholds for the interpretation of I^2 can be misleading since the importance of inconsistency depends on several factors. A rough guide to interpretation is as follows**: 0% to 40%:** might not be important; **30% to 60%:** may represent moderate heterogeneity; **50% to 90%:** may represent substantial heterogeneity; **75% to 100%:** considerable heterogeneity **(Cochrane handbook)**

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Disclosure

Barinder Singh, Gagandeep Kaur, Sumeet Attri, and Akanksha Sharma the authors, declare that they have no conflict of interest

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