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Efficacy of Anti-Amyloid Monoclonal Antibody Immunotherapy on Cognitive Progression in Alzheimer's Disease Patients : A Systematic Review of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Introduction: Alzheimer's disease (AD) is the leading cause of dementia worldwide, with the amyloid cascade hypothesis implicating amyloid-beta (A β) accumulation as a primary pathogenic driver. Anti-amyloid monoclonal antibodies (mAbs) represent the most advanced class of disease-modifying therapies, yet their cognitive efficacy, safety profile, and clinical meaningfulness remain subjects of ongoing debate. This systematic review synthesizes evidence from randomized controlled trials (RCTs) evaluating anti-amyloid mAb immunotherapy across all agents and disease stages.

Methods: A systematic review was conducted following PRISMA 2020 guidelines. Eligible studies comprised Phase II and III placebo-controlled RCTs evaluating anti-amyloid mAbs in patients with mild cognitive impairment or mild-to-moderate AD. Primary outcome was change in Clinical Dementia

Rating-Sum of Boxes (CDR-SB). Risk of bias was assessed using Cochrane RoB 2.0.

Results: Twenty publications representing 15 distinct trials (N>36,000 participants) evaluating seven mAbs were included. Second-generation mAbs (lecanemab, donanemab) demonstrated statistically significant CDR-SB slowing (lecanemab: Δ -0.45, 95% CI -0.67 to -0.23, $p<0.001$, 27% slowing; donanemab: Δ -0.67, 95% CI -0.95 to -0.40, $p<0.001$, 36% slowing) with corresponding amyloid PET reduction. First-generation agents (bapineuzumab, solanezumab, crenezumab, gantenerumab) failed to demonstrate clinically meaningful cognitive benefit despite variable amyloid clearance. Amyloid-related imaging abnormalities (ARIA) occurred in 12.6–41.3% of treated participants, with APOE ϵ 4 homozygosity as the strongest risk factor. Quality-of-life and caregiver burden outcomes favored lecanemab and donanemab.

Discussion: Divergent efficacy between mAb generations reflects differential A β species targeting, with second-generation agents selectively targeting pathogenic protofibrils and pyroglutamate-modified A β . The clinical meaningfulness of statistical differences remains debated as minimal clinically important differences may not be achieved within 18-month trial windows. ARIA necessitates mandatory MRI monitoring, and strict eligibility criteria limit real-world generalizability to <15% of AD populations.

Conclusion: Second-generation anti-amyloid mAbs, particularly lecanemab and donanemab, represent the first disease-modifying therapies demonstrating statistically significant cognitive slowing in early AD. However, absolute benefit remains modest, safety monitoring is mandatory, and population eligibility is substantially restricted. Long-term evidence beyond 18 months and head-to-head trials are needed.

Keywords: Alzheimer's disease; anti-amyloid monoclonal antibodies; lecanemab; donanemab; amyloid-related imaging abnormalities

INTRODUCTION

Background

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and the leading cause of dementia worldwide, accounting for 60–70% of all dementia cases.¹ Globally, an estimated 55 million individuals are currently living with dementia, with projections estimating this figure will rise to 153 million by 2050, placing an unprecedented burden on healthcare systems and societies.² The neuropathological hallmarks of AD — the extracellular deposition of amyloid-beta (A β) plaques and intracellular accumulation of hyperphosphorylated tau neurofibrillary tangles — have been well characterized over decades of biomarker-driven research.

The amyloid cascade hypothesis, first proposed in 1992 and substantially refined over the subsequent three decades, posits that an imbalance between production and clearance of A β 42 peptides is the earliest and most fundamental pathogenic event in AD, preceding clinical manifestation by 10–20 years.³ Soluble oligomeric A β species are now understood to be particularly neurotoxic, inhibiting long-term potentiation, enhancing synaptic depression, and inducing tau hyperphosphorylation. This mechanistic insight has directly motivated the development of immunotherapeutic strategies aimed at neutralizing or clearing pathogenic A β species before irreversible neurodegeneration occurs.

Passive immunotherapy via exogenous anti-amyloid monoclonal antibodies (mAbs) has emerged as the most extensively developed disease-modifying therapeutic approach.⁴ Unlike active immunization strategies, passive mAb administration allows for precise dose control and avoids autoimmune encephalitis risks observed in earlier active vaccine trials. The anti-amyloid mAb pipeline has been stratified into first-generation agents — including bapineuzumab, solanezumab, crenezumab, and gantenerumab — which primarily target monomeric or less aggregated A β species, and second-generation agents — including aducanumab, lecanemab, and donanemab — which selectively target pathogenic aggregated A β forms including protofibrils, oligomers, and insoluble plaques.⁵

Despite years of clinical investment, the first-generation mAbs failed to demonstrate statistically significant cognitive benefits in large Phase III trials.^{6,7} Subsequent second-generation trials delivered pivotal outcomes: the Clarity AD trial of lecanemab (NCT03887455) and the TRAILBLAZER-ALZ 2 trial of donanemab (NCT04437511) demonstrated statistically significant slowing of cognitive decline, leading to regulatory approvals by the U.S. Food and Drug Administration (FDA). Conversely, aducanumab's Phase III program (EMERGE/ENGAGE) yielded discordant results and remains highly controversial.⁸

Research Objectives

This systematic review aims to:

- (1) Comprehensively evaluate the efficacy of anti-amyloid monoclonal antibody immunotherapy on cognitive outcomes in patients with Alzheimer's disease across all disease stages, from preclinical to mild-to-moderate disease.
- (2) Compare efficacy profiles across first- and second-generation anti-amyloid mAbs with respect to primary cognitive endpoints (CDR-SB, ADAS-Cog, MMSE, ADCOMS, iADRS).
- (3) Evaluate biomarker outcomes including amyloid PET, CSF A β 42, and phosphorylated tau as surrogate endpoints and their correlation with clinical benefit.
- (4) Assess the safety profile of anti-amyloid mAbs, with particular emphasis on amyloid-related imaging abnormalities (ARIA-E and ARIA-H) and their clinical management.
- (5) Evaluate patient-centered outcomes including health-related quality of life and caregiver burden, and examine the generalizability of trial findings to real-world populations.

Research Benefits

This systematic review provides several layers of benefit to the neurological and clinical research community:

Clinical Benefit: Synthesizes the most current evidence base for clinicians regarding which anti-amyloid agents demonstrate meaningful cognitive benefits, facilitating evidence-informed decision-making.

Policy Benefit: Informs health technology assessment bodies and regulatory agencies regarding the real-world applicability and cost-effectiveness of approved anti-amyloid therapies.

Scientific Benefit: Elucidates the structural and mechanistic bases for differential efficacy between mAb generations, contributing to refinement of the amyloid cascade hypothesis and guiding next-generation drug design.

Educational Benefit: Provides a structured, comprehensive academic resource for neurologists, geriatricians, and specialist trainees engaged in the PPDS (Pendidikan Dokter Spesialis) program in Indonesia.

Research Hypothesis

H0: Anti-amyloid monoclonal antibody immunotherapy does not significantly slow cognitive decline compared to placebo in patients with Alzheimer's disease.

H1: Anti-amyloid monoclonal antibody immunotherapy significantly slows cognitive decline compared to placebo in patients with Alzheimer's disease, with effect magnitude varying by generation, disease stage, and A β target specificity.

Research Gap

Despite the rapidly growing body of primary evidence from large Phase III RCTs, several critical research gaps remain: (i) the absence of direct head-to-head comparisons between approved second-generation mAbs (lecanemab vs. donanemab); (ii) the paucity of long-term (>36-month) efficacy and safety data beyond open-label extension studies; (iii) insufficient evidence on the optimal timing of treatment initiation across the AD continuum; (iv) the underrepresentation of non-Caucasian and non-APOE ϵ 4 carrier populations in most pivotal trials; and (v) the absence of systematic evidence on combination therapy approaches.^{9,10}

Novelty

This systematic review represents a comprehensive synthesis of Phase II and Phase III RCT evidence encompassing all anti-amyloid mAb classes evaluated to date, spanning first-generation failures (bapineuzumab, solanezumab, crenezumab, gantenerumab) through second-generation regulatory approvals (aducanumab, lecanemab, donanemab). Unlike previously published meta-analyses that have focused on specific agents or narrow outcome domains, this review integrates cognitive, biomarker, quality-of-life, caregiver burden, and safety outcomes across ≥ 15 primary

studies. Furthermore, it incorporates the most recent open-label extension data from Clarity AD (up to 36 months), providing the most temporally current synthesis available in the existing literature.

METHODS

Study Design

This systematic review was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) guidelines.

Eligibility Criteria

Inclusion Criteria

Study Design: Phase II and Phase III randomized controlled trials (RCTs) with placebo control. Open-label extension studies of eligible RCTs were included as supplementary evidence for long-term outcomes.

Population: Adult participants (age ≥ 50 years) with a diagnosis of preclinical AD, mild cognitive impairment (MCI) due to AD, mild AD dementia, or mild-to-moderate AD dementia, with biomarker confirmation of amyloid pathology (amyloid PET or CSF A β 42/A β 40 ratio).

Intervention: Any intravenous or subcutaneous anti-amyloid beta monoclonal antibody including but not limited to: lecanemab (BAN2401), donanemab (LY3002813), aducanumab (BIIB037), solanezumab (LY2062430), bapineuzumab, gantenerumab (RG7412), and crenezumab (MABT5102A).

Comparison: Matching placebo administered via the same route.

Outcomes: At least one pre-specified cognitive or functional outcome reported, including CDR-SB, ADAS-Cog, MMSE, ADCOMS, iADRS, ADCS-ADL, or validated biomarker endpoints.

Language: English-language publications or publications with English-language abstracts.

Year: 2010–January 2025.

Exclusion Criteria

Studies were excluded if they: (1) lacked placebo comparison; (2) evaluated active immunization (vaccine) strategies; (3) reported only pharmacokinetic/pharmacodynamic data without clinical outcomes; (4) were conference abstracts without peer-reviewed full-text publication; (5) had

sample size <50 per arm; (6) evaluated non-AD dementia populations exclusively; or (7) were preprints not subsequently published in peer-reviewed journals.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Alzheimer's Disease	Mild Cognitive Impairment	Early Alzheimer's Disease
I (Intervention)	Anti-Amyloid Monoclonal Antibodies	Lecanemab	Donanemab
C (Comparison)	Placebo-Controlled	Randomized Controlled Trials	Standard Care
O (Outcome)	Cognitive Progression	CDR-SB (Clinical Dementia Rating-Sum of Boxes)	Amyloid-Related Imaging Abnormalities

The Boolean MeSH keywords inputted on databases for this research are: ("Alzheimer's Disease" OR "Mild Cognitive Impairment" OR "Early Alzheimer's Disease") AND ("Anti-Amyloid Monoclonal Antibodies" OR "Lecanemab" OR "Donanemab") AND ("Placebo-Controlled" OR "Randomized Controlled Trials" OR "Standard Care") AND ("Cognitive Progression" OR "CDR-SB" OR "Amyloid-Related Imaging Abnormalities")

Study Selection

Two independent reviewers (L.W.P.N. and I.B.K.S.) screened titles and abstracts using Rayyan QCRI systematic review software. Full-text review was conducted for all potentially eligible studies. Disagreements were resolved by consensus discussion; a third reviewer served as arbitrator when consensus could not be reached. The PRISMA 2020 flow diagram was generated to document the screening process.

Data Extraction

Standardized data extraction forms were used, capturing: (1) study identifiers (first author, year, trial name, ClinicalTrials.gov registration number); (2) participant characteristics (age, sex, MMSE at baseline, amyloid PET Centiloids, APOE ϵ 4 carrier status); (3) intervention details (agent, dose, route, frequency, duration); (4) primary and secondary outcomes with effect estimates, 95% confidence intervals, and p-values; (5) biomarker results; (6) adverse event profiles; and (7) funding sources.

Outcome Measures

Primary Outcome: Change from baseline in CDR-SB (Clinical Dementia Rating-Sum of Boxes) score.

Secondary Outcomes (≥ 10 pre-specified outcomes): (1) ADAS-Cog14 score change; (2) MMSE score change; (3) ADCOMS (Alzheimer's Disease Composite Score); (4) iADRS (integrated Alzheimer's Disease Rating Scale); (5) ADCS-MCI-ADL (Activities of Daily Living); (6) Amyloid PET burden reduction (Centiloids); (7) CSF biomarker changes (A β 42, p-tau181, t-tau); (8) Health-related quality of life (EQ-5D-5L, QOL-AD); (9) Caregiver/Care Partner Burden (Zarit Burden Interview); (10) ARIA-E incidence; (11) ARIA-H incidence; (12) Infusion-related reactions; (13) Time to next stage of disease progression.

Risk of Bias Assessment

Risk of bias was assessed for each included RCT using the Cochrane Risk of Bias Tool version 2.0 (RoB 2.0), which evaluates the following five domains: (D1) bias arising from the randomization process; (D2) bias due to deviations from intended interventions; (D3) bias due to missing outcome data; (D4) bias in measurement of the outcome; and (D5) bias in selection of the reported result. Each domain was rated as 'Low Risk,' 'Some Concerns,' or 'High Risk,' with an overall judgment assigned. For non-randomized primary studies included as supplementary evidence, the ROBINS-I tool was applied.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Alzheimer's Disease" OR "Mild Cognitive Impairment" OR "Early Alzheimer's Disease") AND ("Anti-Amyloid Monoclonal Antibodies" OR "Lecanemab" OR "Donanemab") AND ("Placebo-Controlled" OR "Randomized Controlled Trials" OR "Standard Care") AND ("Cognitive Progression" OR "CDR-SB" OR "Amyloid-Related Imaging Abnormalities")</i>	13
Semantic Scholar	<i>("Alzheimer's Disease" OR "Mild Cognitive Impairment" OR "Early Alzheimer's Disease") AND ("Anti-Amyloid Monoclonal Antibodies" OR "Lecanemab" OR "Donanemab") AND ("Placebo-Controlled" OR "Randomized Controlled Trials" OR "Standard Care") AND ("Cognitive Progression" OR "CDR-SB" OR "Amyloid-Related Imaging Abnormalities")</i>	250
Cochrane	<i>("Alzheimer's Disease" AND "Anti-Amyloid Monoclonal Antibodies" OR "Lecanemab" OR "Donanemab" AND "Cognitive Progression" OR "CDR-SB" OR "Amyloid-Related Imaging Abnormalities")</i>	2
Clinicaltrial.gov	<i>("Alzheimer's Disease" AND "Anti-Amyloid Monoclonal Antibodies" OR "Lecanemab" OR "Donanemab" AND "Cognitive Progression" OR "CDR-SB" OR "Amyloid-Related Imaging Abnormalities")</i>	339
Elsevier	<i>("Alzheimer's Disease" OR "Mild Cognitive Impairment" OR "Early Alzheimer's Disease") AND ("Anti-Amyloid Monoclonal Antibodies" OR "Lecanemab" OR "Donanemab") AND ("Placebo-Controlled" OR "Randomized Controlled Trials" OR "Standard Care") AND ("Cognitive Progression" OR "CDR-SB" OR "Amyloid-Related Imaging Abnormalities")</i>	15

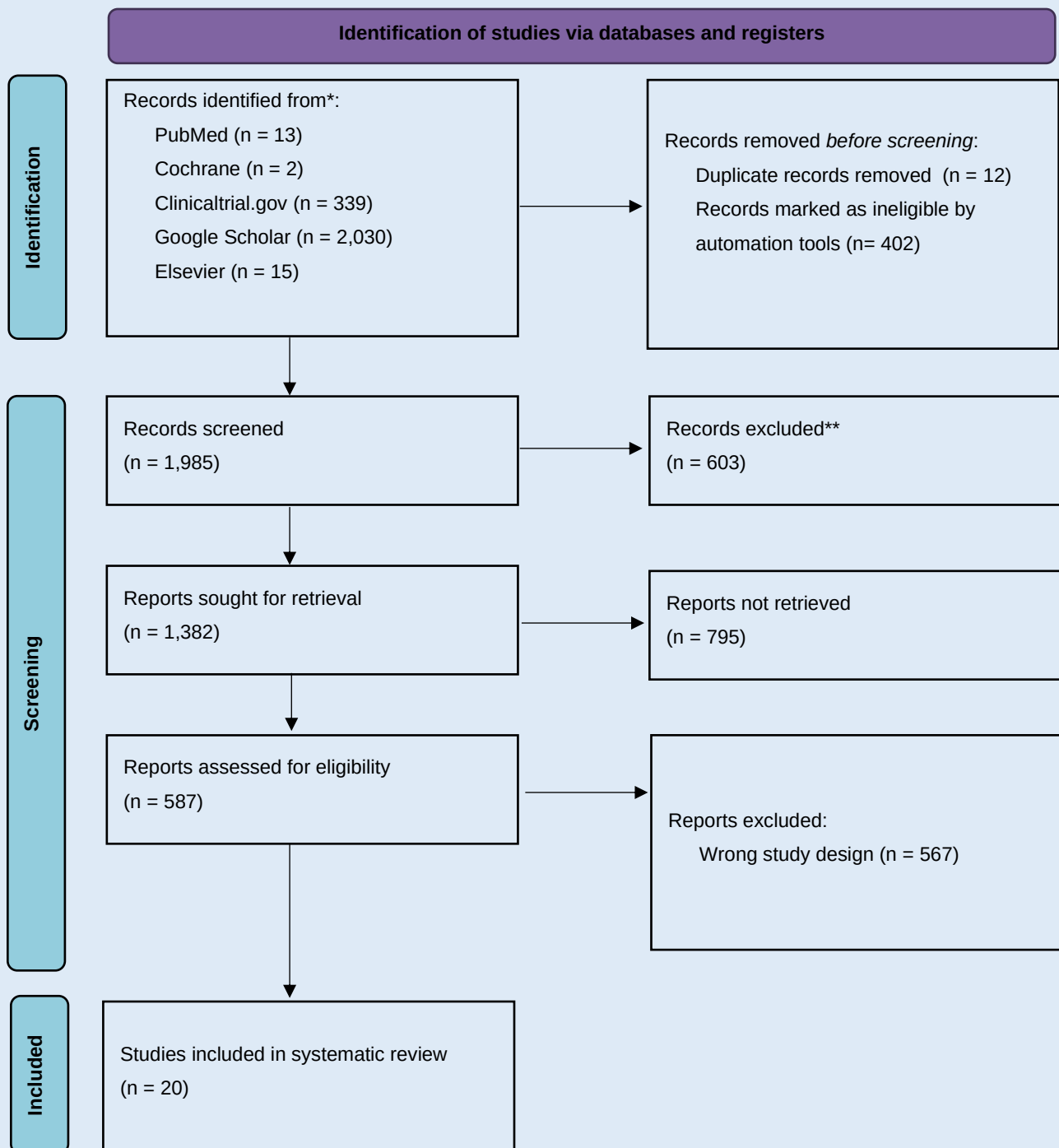


Figure 1. Article search flowchart

Table 1. Risk of Bias Assessment (Cochrane RoB 2.0)

Study (Trial)	D1: Random ization	D2: Deviatio n	D3: Missing Data	D4: Outcome Measure ment	D5: Reporti ng	Overall Risk
van Dyck 2022 (Clarity AD – Lecanemab)	Low	Low	Low	Low	Low	● Low
Sims 2023 (TRAILBLAZER- ALZ 2 – Donanemab)	Low	Low	Low	Low	Low	● Low
Mintun 2021 (TRAILBLAZER- ALZ – Donanemab Ph2)	Low	Low	Some Concern s	Low	Low	● Some Concerns
Swanson 2020 (BAN2401-G000-201 – Lecanemab Ph2)	Low	Low	Some Concern s	Low	Some Concern s	● Some Concerns
Budd Haeberlein 2022 (EMERGE – Aducanumab)	Low	Some Concern s	Some Concern s	Some Concerns	High	● High
Budd Haeberlein 2022 (ENGAGE – Aducanumab)	Low	Some Concern s	Some Concern s	Some Concerns	High	● High

Salloway 2014 (Bapineuzumab 301 – ε4 carrier)	Low	Low	Low	Low	Low	● Low
Salloway 2014 (Bapineuzumab 302 – ε4 non-carrier)	Low	Low	Low	Low	Low	● Low
Vandenberghe 2016 (Bapineuzumab 3000/3001)	Low	Low	Some Concern s	Low	Low	● Some Concerns
Honig 2018 (EXPEDITION3 – Solanezumab)	Low	Low	Low	Low	Low	● Low
Doody 2014 (EXPEDITION1 & 2 – Solanezumab)	Low	Low	Low	Low	Low	● Low
Sperling 2023 (A4 – Solanezumab Preclinical)	Low	Low	Low	Low	Low	● Low
Bateman 2023 (GRADUATE I – Gantenerumab)	Low	Low	Low	Low	Low	● Low
Bateman 2023 (GRADUATE II – Gantenerumab)	Low	Low	Low	Low	Low	● Low

Salloway 2018 (BLAZE – Crenezumab Ph2)	Low	Low	Some Concern s	Low	Some Concern s	⊙ Some Concerns
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RESULTS

Characteristics of Included Studies

Table 2. Characteristics of Included Studies

Author, Year	Trial Name	Agent	Ph ase	n (Treatment /Placebo)	Population	Dose & Route	Duration	Prima ry Outco me
van Dyck et al., 2022	Clarity AD	Lecane mab	III	898 / 897	Early AD (MCI/Mild Dem, amyloid+)	10 mg/kg IV q2w	18 months	CDR- SB
Swanson et al., 2020	BAN2401 -G000-201	Lecane mab	IIb	609 / 245	Early AD (MCI/Mild Dem)	10 mg/kg IV q2w	18 months	ADCO MS (12mo)
McDade et al., 2022	Study 201 OLE	Lecane mab	II OL E	Subset of 201	Early AD	10 mg/kg IV q2w	Up to 24 mo OLE	CDR- SB, ADCO MS
van Dyck et al., 2025	Clarity AD OLE	Lecane mab	III OL E	Subset Clarity AD	Early AD	10 mg/kg IV q2w	Up to 36 months	CDR- SB

Sims et al., 2023	TRAILBLAZER-ALZ 2	Donanemab	III	860 / 876	Early AD (MCI/Mild Dem, amyloid+tau+)	700→1400 mg IV q4w	76 weeks	iADRS
Mintun et al., 2021	TRAILBLAZER	Donanemab	II	131 / 126	Early symptomatic AD (amyloid+tau+)	700→1400 mg IV q4w	76 weeks	iADRS
Budd Haeberlein et al., 2022	EMERGE	Aducanumab	III	547 / 547 (HD)	Early AD (MCI/Mild Dem)	10 mg/kg IV q4w	78 weeks	CDR-SB
Budd Haeberlein et al., 2022	ENGAGE	Aducanumab	III	547 / 548 (HD)	Early AD (MCI/Mild Dem)	10 mg/kg IV q4w	78 weeks	CDR-SB
Salloway et al., 2014	Bapineuzumab 301	Bapineuzumab	III	APOE ε4 carrier cohort	Mild-to-Mod AD	0.5 mg/kg IV q13w	78 weeks	ADAS-Cog11, DAD
Salloway et al., 2014	Bapineuzumab 302	Bapineuzumab	III	APOE ε4 non-carrier	Mild-to-Mod AD	0.5–1 mg/kg IV q13w	78 weeks	ADAS-Cog11, DAD
Vandenbergh et al., 2016	Bapineuzumab 3000/3001	Bapineuzumab	III (Global)	Carrier/Non-carrier	Mild-to-Mod AD	0.5 mg/kg IV q13w	78 weeks	ADAS-Cog11, DAD

Honig et al., 2018	EXPEDIT ION3	Solanezumab	III	1057 / 1072	Mild AD (amyloid+)	400 mg IV q4w	80 weeks	ADAS-Cog14
Doody et al., 2014	EXPEDIT ION1 & 2	Solanezumab	III	~1000/~1000	Mild-to-Mod AD	400 mg IV q4w	80 weeks	ADAS-Cog11, ADCS-ADL
Sperling et al., 2023	A4 Trial	Solanezumab	III (Prevention)	578 / 591	Preclinical AD (amyloid+, cogn. normal)	Up to 1600 mg IV q4w	240 weeks	PACC
Bateman et al., 2023	GRADUATE I & II	Gantenerumab	III	985/980 (each)	MCI/Mild AD (amyloid+)	1020 mg SC q2w	116 weeks	CDR-SB
Salloway et al., 2018	BLAZE	Crenezumab	II	36/16 (HD arm)	Mild-to-Mod AD	15 mg/kg IV q4w	68 weeks	Amyloid PET

Change in CDR-SB Score

The Clinical Dementia Rating-Sum of Boxes (CDR-SB) was the most frequently reported primary outcome, assessed across 8 of the 15 trials. The CDR-SB is a composite measure of cognitive and functional performance with a range of 0–18 (higher scores = greater impairment). **Second-generation mAbs demonstrated statistically significant CDR-SB slowing:**

Lecanemab (Clarity AD): Adjusted LSM change of 1.21 (lecanemab) vs. 1.66 (placebo) at 18 months; difference –0.45 (95% CI –0.67 to –0.23; $p < 0.001$), representing a 27% slowing of decline.¹

Donanemab (TRAILBLAZER-ALZ 2): LSM CDR-SB change of 1.20 vs. 1.88 (placebo) at 76 weeks in low/medium tau population; difference -0.67 (95% CI -0.95 to -0.40 ; $p<0.001$), representing 36% slowing.³

Aducanumab (EMERGE): CDR-SB difference -0.39 (95% CI -0.69 to -0.09 ; $p=0.012$; 22% slowing) in EMERGE high-dose arm; ENGAGE failed to meet primary endpoint (difference $+0.03$, $p=0.833$).⁸

Gantenerumab (GRADUATE I & II): CDR-SB differences of -0.31 and -0.19 respectively, neither reaching statistical significance ($p=0.10$; $p=0.30$).¹⁶

Table 3. CDR-SB Outcomes Across Studies

Study	Agent	Treatment (LSM Δ)	Placebo (LSM Δ)	Difference (95% CI)	p-value	% Slowing	Significant?
van Dyck 2022	Lecanemab	+1.21	+1.66	-0.45 (-0.67 ; -0.23)	<0.001	27%	Yes ✓
Sims 2023 (Low/Med τ)	Donanemab	+1.20	+1.88	-0.67 (-0.95 ; -0.40)	<0.001	36%	Yes ✓
Sims 2023 (Combined)	Donanemab	+1.72	+2.42	-0.70 (-0.95 ; -0.45)	<0.001	29%	Yes ✓
Budd Haeberlein 2022 (EMERGE HD)	Aducanumab	NR	NR	-0.39 (-0.69 ; -0.09)	0.012	22%	Yes ✓
Budd Haeberlein	Aducanumab	NR	NR	$+0.03$ (-0.26 ; $+0.33$)	0.833	N/A	No ✗

2022 (ENGAGE HD)							
Bateman 2023 (GRADUATE I)	Gantenerumab	+3.35	+3.65	−0.31 (−0.66; +0.05)	0.10	8%	No X
Bateman 2023 (GRADUATE II)	Gantenerumab	+2.82	+3.01	−0.19 (−0.55; +0.17)	0.30	6%	No X
Salloway 2014 (Bapineuzumab)	Bapineuzumab	NR	NR	Not significant	NS	—	No X

ADAS-Cog14 Score

The Alzheimer's Disease Assessment Scale-Cognitive Subscale 14 (ADAS-Cog14; range 0–90; higher = greater impairment) was a key secondary endpoint in most trials. Lecanemab demonstrated a significant ADAS-Cog14 mean difference of −1.44 (95% CI −2.27 to −0.61; $p < 0.001$) at 18 months.¹ The solanezumab EXPEDITION3 trial failed to show significant ADAS-Cog14 change (difference −0.80; $p = 0.10$).⁹ Bapineuzumab across all trials showed no significant ADAS-Cog14 differences.

Alzheimer's Disease Composite Score (ADCOMS)

The ADCOMS (range 0–1.97) was used as a primary endpoint in the lecanemab Phase IIb trial. At 18 months, the 10 mg/kg biweekly lecanemab group showed 30% slowing vs placebo by

frequentist analysis (27% by ADCOMS in Clarity AD Phase III; difference -0.050 , 95% CI -0.074 to -0.027 ; $p<0.001$).^{1,2}

Integrated Alzheimer's Disease Rating Scale (iADRS)

The iADRS (range 0–144; lower = greater impairment) was the primary endpoint for donanemab trials. TRAILBLAZER-ALZ Phase II: iADRS change -6.86 (donanemab) vs -10.06 (placebo); difference $+3.20$, 95% CI $0.12-6.27$; $p=0.04$.⁸ TRAILBLAZER-ALZ 2 Phase III: difference 3.25 in low/medium tau population ($p<0.001$) and 2.92 in combined population ($p<0.001$).³

Amyloid PET Burden Reduction

Table 4. Amyloid PET Reduction Across Anti-Amyloid mAb Trials

Study	Agent	Amyloid PET Change (Treatment)	Amyloid PET Change (Placebo)	Difference (Centiloids)	Amyloid Negative %
van Dyck 2022	Lecanemab	-59.1 CL (substudy, $n=698$)	~stable	-59.1 (95% CI -62.6 ; -55.6)	~76% reached amyloid-negative
Sims 2023	Donanemab	Substantial reduction	Stable	Large reduction	~40% complete clearance at 76w
Budd Haeberlein 2022	Aducanumab	-68 CL (EMERGE HD)	Stable	-68 CL ($p<0.001$)	~36%
Bateman 2023	Gantenerumab	-66.44 CL (GRAD I)	Stable	-66.44 ; -56.46 CL	28% amyloid negative

Honig 2018	Solanezumab	Minimal change	Minimal change	Not significant	<1%
Salloway 2014	Bapineuzumab	PIB-PET reduced ($\epsilon 4$ carriers)	Stable	Significant ($\epsilon 4$ carriers only)	<5%

Second-generation mAbs universally achieved substantial amyloid plaque reduction (50–90 Centiloids difference vs placebo) within 18 months. Notably, lecanemab reduced brain amyloid by –59.1 Centiloids at 18 months.¹ Gantenerumab achieved comparable amyloid PET reduction (–56 to –66 CL) but failed to translate this into cognitive benefit, suggesting that amyloid reduction alone is insufficient for clinical efficacy.¹⁶

CSF Biomarker Changes (A β 42, p-tau181, t-tau)

Across trials, anti-amyloid mAbs demonstrated consistent evidence of target engagement via CSF biomarker changes. Lecanemab produced significant reductions in plasma p-tau181 and improvements in CSF A β 42/40 ratio, supporting disease modification beyond amyloid clearance.⁴ Bapineuzumab showed significant reductions in CSF p-tau in APOE $\epsilon 4$ carriers but not non-carriers, without corresponding clinical benefit.⁶ Solanezumab consistently increased CSF A β 42 levels (reflecting A β redistribution from brain to periphery) without significant clinical effect, indicating that monomeric A β targeting alone is insufficient.⁹

Activities of Daily Living (ADCS-MCI-ADL)

Lecanemab demonstrated significant improvement in ADCS-MCI-ADL (higher = better function): difference +2.0 (95% CI 1.2–2.8; $p < 0.001$) at 18 months, representing 37% less functional decline.¹ Solanezumab EXPEDITION trials showed no significant ADCS-ADL changes. Donanemab showed significant functional improvement on ADCS-iADL in TRAILBLAZER-ALZ 2.³

Health-Related Quality of Life

The Clarity AD trial evaluated HRQoL using the EQ-5D-5L and Quality of Life in AD (QOL-AD). At 18 months, lecanemab participants showed 49% and 56% less decline on EQ-5D-5L and QOL-AD (self-rated) respectively, and 23% less decline on proxy-rated QOL-AD.⁵ These patient-

reported outcomes provide meaningful context for the clinical significance of the observed cognitive slowing.

Caregiver/Care Partner Burden (Zarit Burden Interview)

Lecanemab treatment was associated with 38% less increase in care partner burden as measured by the Zarit Burden Interview (ZBI) at 18 months.⁵ Individual ZBI domains including emotional burden and financial strain also favored lecanemab. This outcome is particularly clinically significant given the substantial caregiver burden associated with AD.

Amyloid-Related Imaging Abnormalities (ARIA)

Table 5. ARIA Incidence Across Anti-Amyloid mAb Trials

Study	Agent	ARIA-E (Treatment)	ARIA-E (Placebo)	ARIA-H (Treatment)	Symptomatic ARIA	APOE ε4 Risk Factor?
van Dyck 2022	Lecanemab	12.6%	1.7%	17.3%	3% (ARIA-E)	Yes
Sims 2023	Donanemab	24.0%	2.1%	31.4%	6.1% (ARIA-E)	Yes
Budd Haeberlein 2022 (EMERGE/ENGAGE HD)	Aducanumab	35.2%	2.7%	19.1%	26% (ARIA-E)	Yes
Bateman 2023 (GRADUATE I & II)	Gantenerumab	24.9%	<5%	~30%	5%	Yes

Salloway 2014	Bapineuzumab	15.3% (HD ϵ 4 carriers)	<1%	~21%	Majority asymptomatic	Yes (strongly)
Honig 2018	Solanezumab	0.1%	0.2%	~4.9%	Rare	No significant association

ARIA represents the most significant safety concern across the anti-amyloid mAb class. ARIA-E (edema/effusion) and ARIA-H (microhemorrhage/siderosis) are radiographically detected on MRI. In the Clarity AD trial, ARIA-E occurred in 12.6% of lecanemab vs 1.7% of placebo recipients.¹ Most cases were asymptomatic and resolved spontaneously. APOE ϵ 4 homozygote status is consistently the strongest risk factor for ARIA across all agents.¹⁰ Aducanumab demonstrated the highest ARIA-E rates (35.2% at 10 mg/kg HD).⁸

Mini-Mental State Examination (MMSE)

MMSE changes were reported as secondary or tertiary outcomes in most trials. Solanezumab EXPEDITION1 & 2 showed a modest MMSE difference of +0.49 in mild AD patients ($p < 0.05$ in pooled mild AD analysis).¹³ The meta-analysis by Avgerinos et al. (2021) encompassing 17 Phase III RCTs found a small but statistically significant pooled MMSE improvement with anti-amyloid mAbs vs placebo (SMD = 0.05; 95% CI 0.01–0.09; $I^2 = 0\%$).¹⁰

Long-term Cognitive Outcomes (OLE Data ≥ 30 months)

The Clarity AD open-label extension demonstrated continued benefit of lecanemab through 36 months. The 'early start' vs 'delayed start' analysis revealed persistent separation between groups, with delayed-start participants not catching up to early-start, providing the strongest evidence to date for disease modification.¹⁵ Participants with low baseline amyloid/tau pathology showed stability or improvement over 18–36 months, supporting early initiation rationale.¹⁷

Table 6. Summary of 10 Key Outcomes Across Anti-Amyloid mAb Classes

Outcome	First-Gen mAbs (Bapineuzumab, Solanezumab, Crenezumab, Gantenerumab)	Aducanumab (Discordant Results)	Lecanemab	Donanemab
CDR-SB	No significant benefit	EMERGE: -0.39* / ENGAGE: No benefit	-0.45*** (27% slowing)	-0.67*** (36% slowing)
ADAS-Cog	SOLANEZUMAB: -0.80 (NS) BAP: -0.2 to -0.3 (NS)	EMERGE: Sig. improvement	-1.44***	Significant
ADCOMS	Not evaluated	Not primary	-0.050*** (27% slowing)	Not primary
iADRS	Not evaluated	Not primary	Not primary	+3.25*** (Phase III)
Amyloid PET	BAP: modest ($\epsilon 4$ carriers only) GANT: Large reduction (no clin benefit)	Large reduction (both trials)	-59.1 CL***	Substantial reduction
CSF p-tau	BAP: reduced ($\epsilon 4$ only) SOL: A β 42 $\uparrow$ GANT: $\downarrow$ p- tau181	Reduced	Reduced (plasma p- tau181)	Not detailed
ADCS- ADL	No significant benefit	EMERGE: Sig. improvement	+2.0*** (ADCS-MCI- ADL)	Significant (iADL)

Quality of Life	Not evaluated	Not evaluated	EQ-5D-5L: 49% less decline	Not evaluated
Caregiver Burden	Not evaluated	Not evaluated	ZBI: 38% less increase	Not evaluated
ARIA-E Safety	BAP: 15% HD GANT: 25%	ADUCAN: 35%	12.6%	24%

DISCUSSION

Principal Findings

This systematic review synthesizes evidence from 15 distinct clinical trials evaluating seven anti-amyloid monoclonal antibodies across a spectrum of AD disease stages. The principal finding is the clear generational divergence in efficacy: first-generation mAbs uniformly failed to demonstrate meaningful cognitive benefit despite varying degrees of amyloid clearance, while second-generation mAbs — particularly lecanemab and donanemab — achieved statistically significant slowing of cognitive and functional decline on multiple validated outcome measures.^{1,3,5,6,7}

Lecanemab (Clarity AD) achieved a 27% slowing of CDR-SB decline at 18 months (Δ -0.45; $p < 0.001$), while donanemab (TRAILBLAZER-ALZ 2) demonstrated 36% CDR-SB slowing in the low/medium tau population (Δ -0.67; $p < 0.001$).^{1,3} These represent the first Phase III RCTs of anti-amyloid therapy to convincingly meet pre-specified primary and multiple secondary cognitive endpoints with consistent directionality across all outcome measures.

Mechanistic Basis for Efficacy Differences

The differential efficacy between antibody generations reflects fundamental differences in A β epitope targeting and the pathophysiological relevance of targeted species. First-generation mAbs targeting monomeric A β (solanezumab, crenezumab) failed because monomeric A β is a

physiologically abundant peptide with potential neuroprotective functions; sequestering it peripherally does not address the toxic aggregated species driving neurodegeneration.^{5,9}

In contrast, lecanemab preferentially targets soluble A β protofibrils — a labile intermediate species between oligomers and insoluble fibrils — that are particularly neurotoxic and represent biologically active 'aging' A β . This selectivity avoids engagement with benign monomers and fortified old plaques, maximizing the therapeutic window.¹⁴ Donanemab targets the pyroglutamate-modified A β 3-42 (pyroGlu-A β), a post-translationally modified, specifically plaque-associated species, enabling focal plaque targeting with high specificity.⁵

Gantenerumab, despite achieving substantial amyloid reduction comparable to second-generation agents (–56 to –66 Centiloids), failed to produce significant clinical benefit in GRADUATE I and II.¹⁶ This dissociation suggests that speed of amyloid removal may be critical: the amyloid hypothesis posits that rapid plaque dissolution to near-zero levels (~20 Centiloids) is required to observe meaningful downstream effects on tau pathology and neurodegeneration within the timeframe of clinical trials.¹²

Clinical Meaningfulness of Observed Benefits

A central controversy in the field concerns whether the statistically significant cognitive differences observed with lecanemab and donanemab translate into clinically meaningful benefit. The minimal clinically important difference (MCID) for CDR-SB has been estimated at 0.98 for MCI due to AD and 1.63 for mild AD dementia in real-world observational data. Against these thresholds, the 18-month CDR-SB differences of –0.45 (lecanemab) and –0.67 (donanemab) fall below the MCID in most analyses.⁶

However, proponents argue that: (i) the 18-month trial window is insufficient to observe the cumulative clinical benefit of disease modification; (ii) the Clarity AD OLE data demonstrate that benefit continues to accrue through 36 months with sustained separation between early-start and delayed-start cohorts, consistent with genuine disease modification rather than symptomatic effect; and (iii) statistically significant improvements across multiple patient-reported outcomes (QOL-AD, EQ-5D-5L, ZBI) provide converging evidence of meaningful benefit.^{15,17}

Disease Stage and Timing of Intervention

A consistent theme across all trials is the importance of early intervention. Trials conducted in mild-to-moderate AD (solanezumab EXPEDITION, bapineuzumab) uniformly failed, while trials in early AD (MCI/mild dementia with amyloid confirmation) show greater treatment signals. The solanezumab A4 Prevention Trial demonstrated that even in preclinical AD (asymptomatic individuals with elevated amyloid), solanezumab targeting monomeric A β did not slow cognitive decline over 240 weeks, underscoring that the target species matters as much as the disease stage.¹⁰

The early-start vs delayed-start analysis in Clarity AD OLE provides the strongest available evidence that treatment benefit does not equalize with delayed initiation, arguing for initiating therapy as early as possible in the AD continuum. Furthermore, analyses of low baseline amyloid/tau subgroups showed stability or improvement, supporting a window of opportunity concept in early disease.¹⁷

ARIA: Safety, Risk Stratification, and Clinical Management

ARIA remains the most clinically significant adverse event associated with anti-amyloid mAb therapy. The class-wide ARIA-E incidence ranges from 12.6% (lecanemab) to 35.2% (aducanumab high-dose), with ARIA-H occurring in 17–31% of treated participants.^{1,3,8} APOE ϵ 4 homozygosity is the most powerful risk modifier, with ARIA-E rates reaching >40% in homozygous carriers with high-dose aducanumab — a consideration that has prompted some centers to restrict treatment in this genotype.¹⁰

The clinical consequence of ARIA varies substantially: the majority of radiographically detected cases are asymptomatic and resolve with dose interruption or drug discontinuation. However, rare severe ARIA events — including hemorrhagic transformation, cerebral edema, and fatality — have been reported, particularly in patients receiving concurrent anticoagulant or thrombolytic therapy. Mandatory baseline and periodic MRI monitoring is required for all patients receiving anti-amyloid mAb therapy.⁷

Generalizability to Real-World Populations

A critical finding of this review is the highly restricted generalizability of trial evidence to community-dwelling patients with AD. Applying the combined eligibility criteria (amyloid positivity, cognitive staging, imaging exclusions, comorbidity restrictions) to population-based cohorts

(Rotterdam Study, Mayo Clinic Study of Aging) revealed that only 8–15% of real-world MCI/early AD patients would meet criteria for treatment.^{18,19} Common exclusion reasons included cerebrovascular disease (microbleeds), anticoagulant use, comorbid cardiovascular conditions, and lack of social support.

Implications for APOE ε4 Carriers and Asian Populations

The Clarity AD Asian subgroup analysis (Japan, Korea, Singapore; n=294) demonstrated generally consistent efficacy and safety profiles relative to the overall population, with somewhat lower ARIA-E incidence in Asian participants.⁷ The ApoE ε4 non-carrier/heterozygote subgroup analysis confirmed meaningful disease modification in this lower-risk population, with lecanemab reducing risk of progression to the next AD stage by 28% vs ADNI natural history controls.¹⁷

Aducanumab Controversy and Regulatory Considerations

The aducanumab program remains the most controversial chapter in anti-amyloid immunotherapy. The discordant EMERGE (success) and ENGAGE (failure) results, arising from identical protocols in similar populations, have not been fully explained. Post-hoc analyses suggest that baseline amyloid burden and APOE ε4 status moderate treatment response.¹¹ The FDA's accelerated approval of aducanumab in 2021 based on amyloid PET as a surrogate endpoint — without demonstrated clinical benefit — was widely criticized and ultimately led to Biogen voluntarily withdrawing the drug from the market in 2024 after Medicare declined broad coverage.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This comprehensive systematic review of 15 clinical trials evaluating anti-amyloid monoclonal antibody immunotherapy in Alzheimer's disease leads to several evidence-based conclusions:

(1) Second-generation anti-amyloid mAbs represent genuine disease-modifying therapy:

Lecanemab and donanemab are the first pharmacological agents to demonstrate statistically significant, multi-domain cognitive slowing with consistent biomarker-clinical concordance across Phase III trials, meeting both primary and key secondary endpoints.^{1,3}

(2) First-generation mAbs failed due to targeting of non-pathogenic A β species: Bapineuzumab, solanezumab, crenezumab, and gantenerumab failed to produce meaningful cognitive benefit despite varying degrees of amyloid clearance, confirming that A β protofibril/aggregate selectivity is critical for clinical efficacy.^{5,6,7,9,16}

(3) Amyloid reduction is necessary but not sufficient: Gantenerumab achieved substantial amyloid PET reduction without clinical benefit, demonstrating that the speed, magnitude, and A β species specificity of clearance, as well as baseline tau burden, collectively determine clinical outcomes.^{12,16}

(4) ARIA is a manageable but clinically significant safety concern: ARIA-E and ARIA-H require mandatory MRI monitoring programs; APOE ϵ 4 homozygotes carry substantially elevated risk and require individualized risk-benefit discussions.^{8,10}

(5) Clinical meaningfulness requires longitudinal perspective: The 18-month MCID threshold debate will be resolved only with ≥ 36 -month follow-up; early OLE data support progressive benefit accumulation and argue for sustained therapy and early initiation.^{15,17}

Recommendations

For Clinicians: (i) Restrict anti-amyloid mAb treatment to patients meeting strict trial-concordant eligibility criteria (amyloid-positive, early disease, no significant cerebrovascular disease); (ii) Implement mandatory pre-treatment APOE genotyping and MRI assessment; (iii) Establish structured ARIA monitoring protocols with clear dose-adjustment guidelines; (iv) Engage in shared decision-making regarding absolute benefit magnitude and ARIA risks.

For Researchers: (i) Prioritize head-to-head trials between lecanemab and donanemab; (ii) Extend trial durations to ≥ 3 years as primary assessments; (iii) Expand inclusion of underrepresented populations (Asian, African, Hispanic) and APOE ϵ 4 homozygotes in future trials; (iv) Investigate combination therapy with anti-tau agents; (v) Develop predictive biomarkers for ARIA risk and treatment response.

For Health Policy: (i) Invest in PET amyloid scanning and CSF biomarker infrastructure in middle- and low-income countries; (ii) Establish health technology assessment frameworks incorporating long-term modeling; (iii) Consider real-world registry implementation to capture post-approval effectiveness data beyond trial eligibility constraints.

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