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Updates on pharmacological treatment for Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia, and its rising prevalence is constantly increasing the global health burden. There are currently no curative therapies for AD, and current treatment options provide only modest clinical benefit. Despite numerous clinical trials, there have been no major additions to the AD treatment armamentarium this century. The prevailing pathomechanistic hypothesis for AD begins with abnormal accumulation of amyloid β (Aβ) leading to plaque development, and disease-modifying candidate therapies have largely aimed to disrupt this process. Numerous clinical trials of monoclonal antibodies directed at various stages of Aβ plaque development have yielded mostly negative results; however, recent results suggest that a breakthrough may be on the horizon. The past two years have yielded positive results for three monoclonal antibodies (aducanumab, lecanemab, and donanemab) although questions remain regarding their clinical effectiveness. Additional clarity is needed to determine whether the clinical benefits are great enough to offset the treatment risks and the resource implications for healthcare systems. This review provides a foundational context and update on recent disease-modifying therapies for AD that have reached Phase III clinical trials. Up-to-date information on these therapies will help clinicians better inform their clinical decision-making and the counselling they can offer patients and their carers.

Keywords: dementia, Alzheimer's disease, treatment, amyloid, clinical trials

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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease, with a global prevalence that continues to rise. There are currently 6.1 million individuals with AD in the United States (US) and this is expected to reach 13.8 million by 2060 [1]. Like most neurodegenerative diseases, advancing age is the greatest risk factor in AD and is thought to be the primary driving force behind rising disease prevalence. In 2023, individuals who are 85 years or older account for 33% of all people with AD but this is expected to have risen to 48% by 2060 [1]. The global incidence of AD and other dementias increased by nearly 150% between 1990 and 2019 [2]. These rising figures paint a grim reality for patients, carers, healthcare systems, and the global economy.

Despite these trends, there have been no significant additions to the AD treatment armamentarium since donepezil and memantine were approved by the US Food and Drug Administration (FDA) in 1996 and 2003, respectively. Unfortunately, these medications typically provide only modest benefits to patients. In 2016, AD became the 6th most burdensome disease/injury in the US according to the Global Burden of Disease classification system, and it was the seventh-leading cause of death in the US in 2021 [3, 4]. The need for treatments that can prevent or significantly alter the trajectory of disease has never been greater. A treatment that could delay the onset of AD-related symptoms by five years would result in 41% lower prevalence and 40% lower cost of AD in 2050 [5].

The distinct histopathological features initially witnessed by Dr. Alois Alzheimer include plaques composed primarily of extracellular beta amyloid (Aβ), and neurofibrillary tangles, which consist of intraneuronal phosphorylated tau. Neurological symptoms correlate with the distribution of neurofibrillary tangles rather than Aβ plaques [6]. We now know that Aβ accumulation and plaque formation precede

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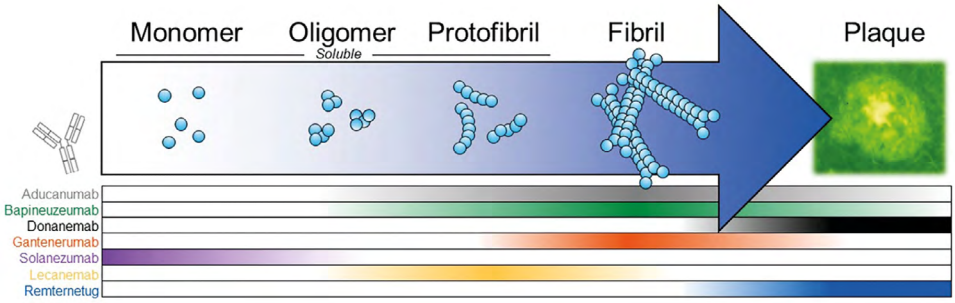

Figure 1. Monoclonal antibody affinity for amyloid β plaque development stages. Illustration of staged amyloid β plaque development and primary affinities for anti-amyloid monoclonal antibodies with Phase III clinical trial results. Bar segment colour intensity approximately correlates with binding affinity of antibody. Image of amyloid plaque visualised with thioflavin staining

tau tangle formation, which precedes neurodegeneration [7]. Some have questioned the validity of this amyloid hypothesis, yet these pathological hallmarks remain the primary focus of disease-modifying treatment trials [8, 9]. Unique treatment side effects have subsequently emerged, including amyloid-related imaging abnormalities (ARIA), which occur more commonly among individuals who carrier the APOE ε4 allele. These individuals are known to have an increased risk of AD [10].

The overall drug development pipeline for AD changes substantially each year, but the group of treatments in Phase III clinical trials remains relatively stable due to long trial durations. Nevertheless, there have been major updates in the status of many drugs currently in large scale trials. After decades of failed therapy trials, it has suddenly become a challenge to remain informed about the status of various treatments as they move through the research and development pipeline. This review aims to provide an update on the current status and trajectory of the disease-modifying treatment landscape for AD.

Anti-amyloid therapies

Deposition of the Aβ protein is the earliest histopathological hallmark of AD, and begins in the neocortex before propagating, in a predictable fashion, to deeper brain structures. Thal et al. [11] characterised the Aβ propagation pattern to involve the CA1 region of the hippocampus and entorhinal cortex (Thal phase 2) before progressing through the thalamus, basal ganglia, and other structures ultimately including the cerebellum (Thal phase 5). Because this deposition pattern is well underway before tau tangle accumulation or neurodegeneration, therapies targetting Aβ have dominated the clinical trial space for nearly two decades. Since the earliest Phase III clinical trials of bapineuzumab, a number of monoclonal antibodies have been developed to target various regions of the Aβ protein with varying degrees of specificity for different stages of Aβ plaque formation (Fig. 1). Unfortunately, every drug failed in its Phase III clinical trial, until 2021.

Aducanumab

Aducanumab (Aduhelm; Biogen, Inc.) is a humanised IgG1 monoclonal antibody that targets aggregated forms of Aβ and is administered as a monthly intravenous (i.v.) infusion. In 2012, a double-blind, placebo-controlled Phase Ib randomised trial (PRIME) of patients with prodromal or mild AD began. Interim analysis of 165 patients who received either the drug or a placebo for one year showed dose-dependent target engagement, based upon significant Aβ plaque reduction on florbetapir PET imaging [12]. While this study was not powered to detect clinical change, there was evidence supporting a dose-dependent slowing of clinical progression based on differences in the change from baseline on the clinical dementia rating scale sum of boxes (CDR-SB) and the Mini Mental State Examination (MMSE) [13]. The most common adverse effect was ARIA, which occurred more often among participants receiving higher drug doses and those who were APOE ε4 allele carriers. ARIA occurred with both vasogenic oedema (ARIA-E) and haemorrhagic (ARIA-H) manifestations, but was symptomatic in a minority of patients.

In 2015, two double-blind, placebo-controlled, parallel-group Phase III randomised clinical trials (EMERGE and ENGAGE) began for individuals with mild cognitive impairment (MCI) or mild dementia due to AD confirmed with amyloid PET. Participants were randomised in a 1:1:1 ratio to receive low dose aducanumab (3 mg/kg), or high dose aducanumab (6 mg/kg), or a placebo [14]. Based on the previous data indicating a greater risk of ARIA among APOE ε4 allele carriers, only non-carriers of the ε4 allele were eligible to receive 10 mg/kg doses. After multiple failed trials indicated that ARIA-E was most often asymptomatic and reversible, the study protocols for EMERGE and ENGAGE were modified to permit APOE ε4 allele carriers to receive the 10 mg/kg dose [15–17].

Table 1. Ongoing or planned phase III/IV trials of disease-modifying therapies for AD

Drug	Trial	Study population	Intervention	Primary endpoint	Expected completion date
Aducanumab	NCT05310071 (ENVISION)	MCI or mild dementia due to AD	i.v. infusion of aducanumab q4 wks	Change from baseline in CDR-SB	10/2026
	NCT05108922 (TRAILBLAZER-ALZ 4)	Early symptomatic AD (CDR-GS 0.5 or 1) & MMSE 20–30)	i.v. infusion of aducanumab or donanemab q4 wks	% of Participants who reach complete amyloid plaque clearance on PET	7/2024
	NCT04241068 Open-Label Extension	MCI or mild dementia due to AD	i.v. infusion of aducanumab q4 wks	AE, serious AE, ARIA-E, ARIA-H	2/2025
Donanemab	NCT05108922 (TRAILBLAZER-ALZ 4)	Early symptomatic AD (CDR-GS 0.5 or 1) & MMSE 20–30)	i.v. aducanumab or donanemab q4 wks	% of Participants who reach complete amyloid plaque clearance on PET.	7/2024
	NCT05026866 (TRAILBLAZER-ALZ 3)	Cognitively normal AD	i.v. donanemab or placebo q4 wks	Change from baseline in CDR-GS.	11/2027
	NCT05508789 (TRAILBLAZER-ALZ 5) *Europe & Asia only	Early symptomatic AD (MMSE 20–28)	i.v. donanemab or placebo q4 wks	Change from baseline on iADRS	6/2027
	NCT05738486 (TRAILBLAZER-ALZ 6)	Early symptomatic AD (MMSE 20–28)	i.v. donanemab or placebo at varying intervals	ARIA-E	5/2025
Lecanemab	NCT04468659 (AHEAD 3-45)	Cognitively normal AD	i.v. lecanemab or placebo q2 wks	A45: Change from baseline in PACC5 A3: Change from baseline in amyloid PET	10/2027
	NCT05269394 (DIAN-TU)	Cognitively normal or MCI with known deterministic AD mutation	i.v. lecanemab & E2814	Change in tau PET	10/2027
	NCT01760005 (DIAN-TU-001)	Cognitively normal or MCI with known deterministic AD mutation	i.v. lecanemab & E2814	Change from baseline in DIAN-MCE	10/2027
E2814	See lecanemab for NCT05269394 & NCT01760005				
Remternetug	NCT05463731 (TRAILRUNNER-ALZ 1)	Early symptomatic AD (MMSE 20–28)	i.v. or SC remternetug or placebo	% of participants who reach complete amyloid plaque clearance on PET	10/2026
Tertomotide	NCT05303701	Severe AD (NINCDS--ADRDA criteria and Korean MMSE ≤ 19)	SC tertomotide or placebo q4 wks then q2 wks	Change from baseline in SIB and CDR-SB	4/2026
Semaglutide	NCT04777396 (EVOKE)	MCI or mild dementia due to AD (CDR-GS 0.5 or 1.0 & MMSE ≥ 22)	Oral semaglutide or placebo daily	Change from baseline in CDR-SB	10/2026
	NCT04777409 (EVOKE Plus)	MCI or mild dementia due to AD (CDR-GS 0.5 or 1.0 & MMSE ≥ 22)	Oral semaglutide or placebo daily	Change from baseline in CDR-SB	10/2026
	NCT05891496	MCI or mild dementia due to AD (CDR-GS 0.5 or 1.0)	SC semaglutide or placebo weekly	Change in gene expression with scRNAseq (CSF and blood)	6/2025

AE — adverse events; ARIA-E — amyloid related imaging abnormalities oedema subtype; ARIA-H — amyloid related imaging abnormalities haemorrhagic subtype; CDR-SB — Clinical Dementia Rating Scale--Sum of Boxes; CDR-GS — CDR-Global Score; CSF — cerebrospinal fluid; DIAN-MCE — Dominantly Inherited Alzheimer's Network-Multivariate Cognitive Endpoint; iADRS — Integated Alzheimer's Disease Rating Scale; i.v. — intravenous; MCI — mild cognitive impairment; NINCDS-ADRDA — National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; PACC5 — Preclinical Alzheimer's Cognitive Composite 5; SC — subcutaneous; SIB — Severe Impairment Battery. *According to clinicaltrials.gov as of 25 July, 2023*

In 2019, an interim analysis predicted that neither trial would meet its primary endpoint of a slowed rate of decline on the CDR-SB. However, data acquired during the time between this announcement and the actual trial stop date indicated that EMERGE met its primary endpoint because participants receiving the highest drug dose (10 mg/kg) showed a significant reduction in decline on the CDR-SB [18]. These participants also met the secondary endpoints of slowed decline on the MMSE, Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), and Alzheimer's Disease Cooperative

Study Activities of Daily Living for Mild Cognitive Impairment (ADCS-ADL-MCI). Based on this, and an exploratory analysis suggesting that ENGAGE participants who received ≥ 10 doses of the 10 mg/kg dose declined more slowly, Biogen applied for approvals from the US FDA, the European Union, and Japan. Despite the recommendation of an FDA advisory panel to deny approval, based on the drug's inability to meet the primary endpoint in both Phase III clinical trials, the FDA approved aducanumab in the summer of 2021. The FDA also required a Phase IV confirmatory trial that would eventually be titled ENVISION (Tab. 1).

As the first disease-modifying therapy approved for AD, aducanumab was initially priced at $56,000 per annum. Biogen Inc. lowered the drug price to $28,200 partially out of growing concern for the economic implications of prescribing such an expensive medication in a large percentage of the population, most of whom are enrolled in Medicare (in the US). Based on this information, and the need for additional neuroimaging surveillance, the estimated annualised Medicare costs were $7 billion if prescribing strictly adhered to the clinical trial inclusion criteria [19]. This figure rose steeply to $37.4 billion when taking into account off-label prescribing. Ultimately, the US Centres for Medicare and Medicaid Services (CMS) restricted coverage to individuals in clinical trials. In 2022, Biogen Inc. withdrew its Marketing Authorisation Application to the European Medicines Agency. Aducanumab remains available in the US only for patients who are able to pay directly out of their own pockets, given the lack of insurance coverage.

In addition to ENVISION, which will conclude in 2026, ongoing studies of aducanumab include an open label extension of EMERGE/ENGAGE, a head-to-head comparison with donanemab, and a phase Ib open-label study to evaluate the safety and feasibility of opening the blood-brain barrier in conjunction with aducanumab therapy (Tab. 1) [20].

Donanemab

Donanemab (Eli Lilly & Co.) is a humanised IgG1 monoclonal antibody that directly targets Aβ plaques. Results from a Phase I study of participants with MCI or mild dementia due to AD demonstrated safety over a 12-week follow-up period [21]. Participants received a single i.v. infusion and only the highest dose (10 mg/kg) yielded amyloid reduction at study completion. A subsequent randomised placebo-controlled Phase II study (TRAILBLAZER-ALZ) included 257 participants with MCI or mild dementia due to AD (confirmed with amyloid and tau PET positivity). Participants in the treatment arm received 700 mg for the first three monthly infusions before doubling the dose [22]. At the completion of a 76-week study period, the treatment group showed a statistically significant 32% reduction in the rate of decline on the Integrated Alzheimer's Disease Rating Scale (iADRS). There were no differences among secondary outcomes including CDR-SB, ADAS-Cog_{13}, Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living Inventory (ADCS-iADL), and MMSE, nor changes in amyloid or tau brain PET signals.

Post-hoc analyses of TRAILBLAZER-ALZ showed that the rate of amyloid reduction at 24 weeks correlated with the amount of baseline amyloid, and modelling suggested that amyloid would not reaccumulate to the AD threshold for nearly four years after drug discontinuation [23]. Among participants with complete amyloid clearance, tau accumulated more slowly. A separate analysis of study participants found that APOE ε4 allele carriers were four times more likely than non-carriers to have ARIA-E by 24 weeks [24]. Participants receiving donanemab showed significant reductions in plasma pTau217 and glial fibrillary acidic protein, although neurofilament light chain (NfL) was not significantly changed [25]. An open-label extension including a one-month validation of home assessments is expected to be complete by early 2024 [26].

TRAILBLAZER-ALZ2 is a Phase III, double-blind, placebo-controlled study of 1,736 participants with prodromal AD and mild dementia due to AD (confirmed with 18F flortaucipir and florbetapir PET scans). The study met its primary endpoint of a slowed rate of change from baseline on the iADRS following 76 weeks of treatment. After one year, 47% of participants receiving donanemab showed no decline on the CDS-SB compared to only 29% of participants receiving a placebo [27]. Among all participants receiving donanemab, there was a 22.3% slowing compared to the placebo. Study investigators also stratified participants based upon tau burden and demonstrated that those with low/medium tau showed an even greater benefit from therapy (35.1% slowing). These important findings suggest that there are subgroups of patients that will respond more favourably to this therapy and may have implications for future therapy decisions.

In 2021, Eli Lilly & Co. began TRAILBLAZER-ALZ3, which is a double-blind, randomised, placebo-controlled trial of cognitively normal participants at risk for developing symptomatic AD based upon positive plasma p-tau-217. The primary outcome measure is the time to clinical progression measured by the CDR global score (CDR-GS) after 3.5 years of follow-up. A unique aspect of this trial is the implementation of the modified Telephone Interview for Cognitive Status (TICS-M) (Tab. 1) [28]. TRAILBLAZER-ALZ4 is a head-to-head comparison of donanemab versus aducanumab with respect to amyloid plaque clearance in participants with early symptomatic AD, defined as a CDR-GS of 0.5–1 and MMSE of 20–30. The estimated study completion is mid-2024 (Tab. 1) [29]. TRAILBLAZER-ALZ5 has an identical trial design to that of TRAILBLAZER-ALZ2, but will include only study sites in Europe (including Poland) and Asia (Tab. 1) [30].

Gantenerumab

Gantenerumab (F. Hoffmann-La Roche) is an IgG1 antibody directed against Aβ fibrils that is administered by subcutaneous (SC) injection. The SCarlet RoAD trial was a randomised,

double-blind, placebo-controlled phase II study assessing the safety and efficacy of gantenerumab administered in low (105 mg) or high (225 mg) doses every four weeks to participants with prodromal AD for two years [31, 32]. This trial was also the first to include amyloid biomarker confirmation as an inclusion criterion [16]. Two years into the study, results from a Phase I study of gantenerumab supported Aβ clearance [33]. Subsequently, Roche converted SCarlet RoAD into a Phase III study and began a fresh Phase III study (Marguerite RoAD) featuring only participants with mild AD dementia. Two years later, a futility analysis of SCarlet RoAD indicated that the primary outcome measure was unlikely to be met. Study investigators attributed this negative result to low drug doses, which were chosen to minimise the risk of ARIA. However, Phase III trials of bapineuzumab indicated that ARIA-E tended to be asymptomatic and was more likely among APOE ε4 allele carriers [34, 35]. As a result of the SCarlet RoAD futility analysis, dosing was interrupted, but participants continued to be followed up for safety and efficacy. Recruitment for Marguerite RoAD was stopped, but dosing continued.

In 2013, modelling estimations of the AD neuroimaging initiative (ADNI) database clustered AD patients into fast-progressing and slow-progressing subpopulations [36]. By applying this model to the SCarlet RoAD cohort, the trial investigators concluded that fast progressors demonstrated a dose-dependent slowing of decline in ADAS-Cog_{13}, Cambridge Neuropsychological Test Automated Battery (CANTAB), and MMSE. Taken together with significant reductions in levels of CSF t-tau and p-tau as well as positive Phase Ib results for high-dose aducanumab, it was speculated that gantenerumab was dosed too low [12, 16]. Subsequently, SCarlet RoAD and Marguerite RoAD were both converted into open label extensions to test the safety of higher doses up to 1,200 mg [37, 38]. An amyloid PET sub-study showed that 51% and 80% of participants were below the amyloid positivity threshold at two and three years, respectively [39, 40].

In 2018, the GRADUATE I and GRADUATE II parallel, randomised, double-blind, placebo-controlled trials began across 30 different countries. These twin trials assessed the efficacy and safety of subcutaneous (SC) injections of gantenerumab initially dosed at 120 mg every four weeks and increased to 510 mg every two weeks by the 9th month regardless of APOE allele status [31]. In November 2022, Roche announced that both GRADUATE studies did not meet their primary endpoint of a slowed rate of decline on the CDR-SB [41]. The following month, Roche presented unpublished data at the Clinical Trials on Alzheimer's disease conference that indicated that gantenerumab cleared fewer Aβ plaques than anticipated. The company then discontinued SKYLINE, a Phase III secondary prevention trial, that had begun in early 2022 [42].

In 2012, the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) began a randomised, placebo-controlled, Phase II/III trial (DIAN-TU-001) testing gantenerumab and solanezumab in asymptomatic (CDR 0) and mildly symptomatic (CDR 0.5) carriers of mutations in *APP, PSEN1,* or *PSEN2* genes [43]. The study failed to reach its primary endpoint of showing a difference compared to a placebo on the DIAN Multivariate Cognitive End Point (DIAN-MCE), which is a composite metric of cognition [44]. While solanezumab showed no significant improvements on disease biomarkers, gantenerumab reduced amyloid plaques, CSF t-tau, phospho-tau181, and slowed increases in NfL levels [44]. An open-label extension continued with gantenerumab. Initially, the DIAN-TU investigators were planning to launch a primary prevention trial (DIAN-TU-002) of gantenerumab with an anti-tau agent; however, this was halted after results of DIAN-TU-001 and the GRADUATE studies were released, and Roche discontinued development of the drug in its current form. Roche is now developing a new version (trontinemab) to enhance blood-brain barrier penetration.

Solanezumab

Solanezumab (Eli Lilly & Co.) is a humanised monoclonal IgG1 antibody directed against soluble Aβ delivered by monthly i.v. infusions. Phase III randomised, placebo-controlled clinical trials of solanezumab, including EXPEDITION-1 and EXPEDITION-2, included more than 2,000 participants with mild-to-moderate AD. Primary outcome measures of ADAS-Cog_{11} and ADCS-ADL showed no significant difference compared to a placebo [45]. A subsequent double-blind, placebo-controlled phase III trial (EXPEDITION-3) limited enrollment to participants with mild AD, but also failed to show a significant slowing of cognitive decline measured on the ADAS-Cog14 [15]. Despite these disappointing results, a positive finding was the rare occurrence of ARIA that contributed to other study investigators deciding to increase dosages in other anti-amyloid monoclonal antibody trials, i.e. EMERGE and ENGAGE. Solanezumab also failed to slow the rate of cognitive decline among participants in DIAN-TU-001 as previously discussed (see gantenerumab section) [44].

In 2014, Lilly began the A4 (Anti-Amyloid Treatment in Asymptomatic AD) Phase III clinical trial with a primary outcome measure of change in the Preclinical Alzheimer's Cognitive Composite (PACC) score. In March 2023, Lilly announced that despite quadrupling the initial dosage, an adjustment made in response to EXPEDITION-3 showing low ARIA rates, four years of treatment had not slowed cognitive decline, nor reduced the risk of progression to symptomatic AD, nor resulted in the clearance of Aβ plaque. There are currently no active or planned studies featuring solanezumab (Tab. 1).

Lecanemab

Lecanemab (Eisai Co., Ltd.) is a humanised IgG1 monoclonal antibody that binds soluble Aβ protofibrils and is administered by monthly i.v. infusions. Initial human Phase I studies of lecanemab, at that time named BAN2401, found dose tolerability up to 10 mg/kg every two weeks among

participants with mild-to-moderate AD [46]. A dose exploration Phase II study assessed participants with early-stage AD (NIA-AA criteria), MCI due to AD, or probable AD (NIA-AA criteria) with amyloid PET confirmation. Despite a Bayesian adaptive design, full enrollment of 854 participants was required because this study failed to meet either its primary endpoint or futility conditions at any of the 17 interim analyses [47]. The primary endpoint required 80% probability of ≥ 25% reduction in clinical decline at 12 months on the Alzheimer's Disease Composite Score of cognitive scores (ADCOMS) [48]. While the primary endpoint was not met, Bayesian and frequentist analyses of secondary endpoints at 18 months indicated that 10 mg/kg biweekly lecanemab decreased signal on amyloid PET and decreased the rate of decline on clinical measures (ADCOMS, ADAS-Cog14, CDR-SB) [49]. A 24-month open-label extension of 10 mg/kg biweekly dosing began after a drug-free gap (average of 24 months) during which AD biomarkers, particularly plasma Aβ/40 ratio and p-tau181 levels, began to return to pre-treatment levels while clinical differences from the placebo persisted. Resuming lecanemab resulted in a significantly reduced amyloid plaque and rate of cognitive decline [50].

In 2019, Eisai began a double-blind, Phase III clinical trial (Clarity AD) that enrolled 1,795 participants with MCI or mild dementia due to AD (CSF or PET confirmed), who were randomised to receive i.v. lecanemab 10 mg/kg or a placebo every two weeks. In January 2023, published results showed that lecanemab met its primary endpoint of slowing the rate of decline on CDR-SB at 18 months compared to the placebo. The difference in adjusted least-squares mean change from baseline was -0.45 in favour of lecanemab [51]. Secondary endpoints indicated greater reductions in brain amyloid burden and drug-favouring differences for the ADAS-Cog_{14}, ADCOMS, and ADCS-MCI-ADL score. The most common adverse event was infusion-related reactions, which occurred in 26.4% of participants. ARIA-E occurred in 12.6% of participants. More than half of these participants were homozygous for the APOE ε4 allele. Among all APOE ε4 homozygotes, nearly one in three experienced ARIA-E, although less than 10% were symptomatic. ARIA-H occurred in 17.3% of patients receiving lecanemab compared to 9.0% receiving a placebo; however, symptomatic cases only occurred in 0.7% and 0.2% of participants receiving lecanemab or a placebo, respectively.

While Clarity AD is the first unequivocally positive Phase III clinical trial of an anti-amyloid monoclonal antibody, the question remains as to whether the statistically significant findings are clinically significant. A retrospective analysis of the National Alzheimer's Coordinating Centre Uniform Data Set indicated that a minimal clinically important difference (MCID) in CDR-SB is 0.98 and 1.63 for MCI and mild dementia due to AD, respectively [52]. A 3-year multicentre analysis of participants in the Alzheimer's Disease Cooperative Study indicated that the 12-month MCID for CDR-SB in MCI is 1.0–2.5 [53]. Lecanemab's annual difference was only 0.45 and while this may translate into clinical significance over several years, long-term follow-up data is needed for confirmation. Additional concerns have been raised regarding study methodology and interpretation of results, such as the effect of functional unblinding due to adverse events like ARIA [54]. The US FDA approved lecanemab through the Accelerated Approval Programme and granted full approval in July 2023. The European Medicines Agency is currently reviewing a regulatory application for lecanemab [55]. While the US Veterans Health Administration has agreed to pay the $26,500 drug cost, the US Centres for Medicare & Medicaid Services (CMS) is expected to make coverage decisions after the FDA's final approval verdict. It is important to consider ancillary costs associated with providing lecanemab. These should include MRI surveillance for ARIA, procedural costs associated with administering i.v. infusions, and potential costs associated with managing infusion-related reactions and therapy-related adverse events, e.g. ARIA [56]. Fortunately, ARIA is typically asymptomatic; however, clinicians should carefully consider the risks and potential benefits when determining whether anti-amyloid therapy should be continued and/or supportive therapies, e.g. steroids, should be administered [56, 57]. An estimated 5.4 million Europeans will be eligible for lecanemab and the associated treatment costs will probably exceed 133 billion EUR per year if European drug prices are similar to those of the US [58].

Ongoing trials of lecanemab include the Clarity AD open-label extension, which has reported three deaths due to haemorrhage. Two of these individuals received blood thinners and the third had preexisting amyloid angiopathy [59]. In 2020, the Alzheimer's Clinical Trial Consortium (ACTC) began AHEAD 3-45, which is a 4-year Phase III study of lecanemab in cognitively normal participants with elevated brain amyloid [60]. AHEAD 3-45 consists of two sub-studies. The A3 sub-study includes a target enrollment of 400 participants whose amyloid PET is below the positivity threshold. Participants are randomised to receive monthly i.v. infusions of a placebo or lecanemab 5 mg/kg during weeks 0 to 4, and 10 mg/kg thereafter. The primary outcome measure is a change in amyloid PET after four years of treatment. The A45 sub-study plans to enroll 1,400 participants with positive amyloid PET scans. A45 participants are randomised to receive a biweekly placebo or lecanemab 5 mg/kg during weeks 0 to 6 and 10 mg/kg from weeks 8 to 94 followed by monthly 10 mg/kg until study completion. The primary outcome measure is a change from baseline of the PACC5 after four years of treatment.

Remternetug

Remternetug (Eli Lilly & Co.) is a monoclonal antibody that targets a pyroglutamated form of Aβ aggregated in amyloid plaques like donanemab, with the key difference that remternetug can be administered via SC injection or i.v. infusion. In 2020, a Phase I study began enrolling participants with clinically diagnosed MCI due to AD, dementia due to AD,

and healthy volunteers. Participants would be randomised to receive remternetug (i.v. or SC), in escalating doses, or a placebo. The primary outcome measure is the occurrence of one or more serious adverse events after 61 weeks of drug/placebo. Secondary outcome measures include pharmacokinetic properties (maximum concentration and area under the concentration vs. time curve) and a change from baseline in florbetapir PET signal [61]. In 2023, Lilly presented interim data at the annual AD/PD Conference showing dose-dependent plaque reduction [62]. They also showed that every study participant receiving the highest dose fell below the amyloid PET positivity within three months. All ARIA occurrences occurred in APOEε4 carriers. This study is expected to run until the middle of 2024.

In 2022, Lilly launched a Phase III, randomised, double-blind, placebo-controlled study (TRAILRUNNER-ALZ1) to evaluate remternetug in participants with early symptomatic AD. Participants had to have gradual and progressive cognitive decline for at least six months prior to screening, score within the range of 20-28 on the MMSE, and have a p-tau and amyloid PET profile consistent with AD [63]. This study will enroll 600 participants, who will receive remternetug or a placebo administered in either SC injection or i.v. infusion for one year followed by a one year cross-over extension period. The study will enroll an additional 640 participants into an addendum safety cohort. These participants will not participate in the extension period. The study's primary outcome measure is a difference in the percentage of participants who reach amyloid plaque clearance on amyloid PET. Secondary outcomes include other amyloid PET-related metrics, observed serum trough concentration of remternetug, and anti-drug antibody detection. TRAILRUNNER-ALZ1 has an estimated completion date of October 2026.

Other pharmacological therapies

E2814

E2814 (Eisai Co., Ltd.) is a humanised monoclonal-antibody directed against an epitope within the microtubule-binding domain of the of 4R and 3R repeat tau isoforms administered by i.v. infusion [64]. A Phase I trial (NCT04231513) to test safety and tolerability in healthy volunteers was completed in 2020 with no evidence of drug-related adverse events [65]. Using liquid chromatography-mass spectrometry, the investigators identified a dose-related increase in antibody-associated tau that persisted for at least one month indicating target engagement [66]. In 2021, E2814 was chosen to be used with lecanemab in the DIAN-TU-001 prevention trial [67] to assess symptomatic (MCI or mild dementia) and asymptomatic populations. The symptomatic population are receiving open-label biweekly lecanemab infusions for 24 weeks after which they will be randomised to receive lecanemab plus either intravenous E2814 or a placebo. The asymptomatic population are being randomised to begin the study with either E2814 or a placebo. After one year, open label lecanemab will be added to all participants. The primary outcome measure is a change in tau PET signal from week 24 to week 104 and to week 208 for the symptomatic population. Secondary outcome measures include changes in CDR-SB, a cognitive composite, amyloid PET, and CSF NfL for symptomatic participants. Secondary outcome measures for the asymptomatic population include a change in CSF p-tau217/t-tau ratio and CSF NfL. Study results are expected in 2027. These results are being eagerly anticipated as it has been proposed that combination therapies, e.g. anti-amyloid plus anti-tau, may prove more effective [68].

Tertomotide

Tertomotide (GemVax & KAEL Bio), also known as GV1001 or RIAVAXTM, was initially developed as a peptide vaccine that targets telomerase reverse transcriptase (TERT), which is highly expressed by many cancers. Although a Phase III trial to treat pancreatic cancer was negative, the drug has been repurposed to treat AD based on neuroprotective effects against $A\beta_{25-35}$ oligomer in rodent neural stem cells [69, 70]. In rodents treated with hydrogen peroxide, tertomotide reduced free radical levels and restored expression of survival-related proteins while reducing expression of those proteins associated with cellular death [71].

In 2019, a phase II, double-blind, parallel-group, placebo-controlled, 6-month randomised clinical trial of participants with moderate-to-severe AD began in Korea. Ninety-six participants were randomised in a 1:1:1 fashion to receive four weekly SC injections of low-dose tertomotide, or high-dose tertomotide, or a placebo followed by 10 injections every two weeks. The study met its primary endpoint of a change in the Severe Impairment Battery (SIB) from baseline to 24 weeks [72]. While secondary endpoints, including change on the neuropsychiatric inventory (NPI), ADCS-ADL, and CDR-SB, trended similarly to the SIB, only NPI changes reached statistical significance. The treatment and placebo groups did not differ with respect to the incidence of adverse events.

Currently, a multicentre, randomised, double-blind, placebo-controlled, parallel-design Phase II study in the US is following participants with mild-to-moderate AD randomised to low/high dose tertomotide or a placebo. The primary outcome measure is a change from baseline in ADAS-Cog_{11} after one year [73]. This study is expected to complete by September 2024. In early 2022, a Korean Phase III study began to assess participants with moderate-to-severe AD with an MMSE score ≤ 19 [74]. Study participants were randomised to receive four weekly SC injections of low/high dose tertomotide or a placebo, then 10 injections administered every other week followed by an open extension phase of high dose tertomotide for 49 weeks. The primary outcome measure is a change from baseline in the SIB and CDR-SB. This study is set to complete in early 2026.

Semaglutide

Semaglutide (Novo Nodisk A/S) is a synthetic, long-acting analogue of glucagon-like peptide-1 that is currently used to treat diabetes under the brand names Ozempic™ and Rybelsus™. Based on studies showing that GLP-1 crosses the blood-brain barrier and may improve learning and memory in rodents, theories have emerged regarding a neuroprotective effect in neurodegenerative diseases, e.g. AD and Parkinson's disease (PD) [75–78].

In 2021, a randomised, double-blind, placebo-controlled Phase III study (EVOKE) of semaglutide began for participants with early AD (MCI or mild dementia with AD biomarker confirmation) [79]. Study participants were randomised to receive either once daily oral semaglutide (14 mg) or a placebo for up to 173 weeks. The primary outcome measure is a change in the CDR-SB after two years of treatment. Secondary outcome measures include ADCS-ADL-MCI, time to dementia conversion, ADCOMS, MMSE, NPI, c-reactive protein level changes, and others. A nearly identical Phase III study (EVOKE Plus) will include different cognitive measures, e.g. Montreal Cognitive Assessment and the ADAS-Cog13 [80]. Both EVOKE and EVOKE plus will have a one year extension phase, and are expected to complete in late 2026.

Conclusion

After years that have witnessed many failed Phase III clinical trials, there now appear to be encouraging signs given recent positive results for two anti-amyloid monoclonal antibodies. While questions remain regarding the clinical significance, associated risks, and burden to healthcare systems, many patients are understandably eager to have options at their disposal. The impact that these therapies will have on the AD treatment landscape remains to be seen. This review provides a foundation upon which clinicians can build so that they can stay abreast of updates in this ever-changing field.

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