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REVIEW ARTICLE

Alzheimer's disease drug development pipeline: 2022

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Abstract

Introduction: Alzheimer's disease (AD) represents a global health crisis. Treatments are needed to prevent, delay the onset, slow the progression, improve cognition, and reduce behavioral disturbances of AD. We review the current clinical trials and drugs in development for the treatment of AD.

Methods: We searched the governmental website clinicaltrials.gov where are all clinical trials conducted in the United States must be registered. We used artificial intelligence (AI) and machine learning (ML) approaches to ensure comprehensive detection and characterization of trials and drugs in development. We use the Common Alzheimer's Disease Research Ontology (CADRO) to classify drug targets and mechanisms of action of drugs in the pipeline.

Results: As of January 25, 2022 (index date for this study) there were 143 agents in 172 clinical trials for AD. The pipeline included 31 agents in 47 trials in Phase 3, 82 agents in 94 trials in Phase 2, and 30 agents in 31 trials in Phase 1. Disease-modifying therapies represent 83.2% of the total number of agents in trials; symptomatic cognitive enhancing treatments represent 9.8% of agents in trials; and drugs for the treatment of neuropsychiatric symptoms comprise 6.9%. There is a diverse array of drug targets represented by agents in trials including nearly all CADRO categories. Thirty-seven percent of the candidate agents in the pipeline are repurposed drugs approved for other indications. A total of 50,575 participants are needed to fulfill recruitment requirements for all currently active clinical trials.

Discussion: The AD drug development pipeline has agents representing a substantial array of treatment mechanisms and targets. Advances in drug design, outcome measures, use of biomarkers, and trial conduct promise to accelerate the delivery of new and better treatments for patients with AD.

KEYWORDS
aducanumab, Alzheimer's disease, amyloid, biomarkers, clinical trials, Common Alzheimer's Disease Research Ontology (CADRO), donanemab, drug development, inflammation, lecanemab, pharmaceutical companies, repurposed drugs, tau

Highlights

- There are 143 drugs in the current Alzheimer's disease (AD) drug development pipeline.
- Disease-modifying therapies represent 83.2% of the candidate treatments.
- Current trials require 50,575 participants who will donate 3,878,843 participant-weeks to clinical trials.
- The biopharmaceutical industry sponsors 50% of all clinical trials including 68% of Phase 3 trials.
- Sixty-three percent of Phase 3 trials and 46% of Phase 2 trials include non–North American clinical trial site locations indicating the global ecosystem required for AD drug development.

1 | INTRODUCTION

Alzheimer's disease (AD) is increasing as the size of the aged population grows.[1] In the United States there are currently 6.2 million individuals with AD dementia and the number will reach 12.7 million by 2050. In addition to those with AD in the dementia stages, there are ≈10 million individuals in the United States with mild cognitive impairment (MCI), half of whom (5 million) have MCI due to AD. The total number of persons in the United States with symptomatic forms of AD—MCI due to AD and AD dementia—is 11.2 million.[1] The estimated 2021 cost of caring for those with Alzheimer's disease and related dementias (ADRD) was $355 billion. The world-wide prevalence of AD dementia will triple from its current 50 to 150 million by 2050 with most of those affected living in low- and middle-income countries.[2]

The need for therapy to prevent, delay the onset, slow the progression, and improve the symptoms of AD is compelled by the rising number of those with AD and the growing public health crisis posed by the disease. Advances in therapy are being achieved; aducanumab, the first disease-modifying therapy (DMT) to be approved for AD, became available on the market for those with MCI due to AD and mild AD dementia in 2021. Aducanumab is an anti-amyloid monoclonal antibody, and two more monoclonal antibodies (donanemab and lecanemab) are under review by the US Food and Drug Administration (FDA).[3–5] Additional new treatments for AD may become available in the foreseeable future.

We review the drugs in current clinical trials for AD. We present data from analyses of the clinicaltrials.gov registry, noting agents in Phase 1, 2, and 3; we describe their mechanism of action (MoA) and major trial characteristics. Our goal is to provide an update on agents being developed for AD and to present information on progress in the field of AD therapeutic development. The report follows the strategy developed in previous annual reviews of the AD pipeline.[6–11] The current report used more advanced analytic tools than previously applied including artificial intelligence (AI) and machine learning (ML) to automate our interrogation of clinicaltrials.gov.

2 | METHODS

We used the US National Library of Medicine of the National Institutes of Health (NIH) clinical research registry, clinicaltrials.gov, as the source of information for this review. Beginning in 2007 the "Common Rule" governing clinicaltrials.gov required registration for studies that meet the definition of an "applicable clinical trial" (ACT). ACTs include controlled clinical investigations of any FDA-regulated drugs, biological therapies, or devices for any disease or condition.[12] Review of studies of clinicaltrials.gov indicate that compliance with the common rule is high and most ACTs are registered appropriately.[13,14] The United States has more clinical trials than any other country, and clinicaltrials.gov includes most but not all therapies currently in clinical trials for AD globally.[10] A recent review showed that this registry includes far more trials than any other of the 18 registries reviewed.[15] Based on this information, the current review can be regarded as a comprehensive but not exhaustive analysis of clinical trials of therapies for AD.

The index date for this review is January 25, 2022, and the tables and text apply to the information available on that date. We include all trials of agents in Phases 1, 2, and 3. We collect information on the trial agent; trial title; trial number assigned on clinicaltrials.gov; start date; projected end date; actual end date, if completed or terminated; primary completion date; calculated trial duration; duration of treatment exposure; calculated recruitment period; number of subjects planned for enrollment; number of arms of the study (usually a placebo arm and one or more treatment arms with different doses); whether a biomarker was described as an entry criterion or an outcome; whether the agent was repurposed; subject characteristics (e.g., allowable Mini-Mental State Examination [MMSE] range); and sponsorship (a biopharmaceutical company, NIH with academic medical centers, public–private partnership, or "other"). We included trials labeled as recruiting, active but not recruiting (e.g., trials that have completed recruitment and are continuing with the exposure portion of the trial), enrolling by invitation (e.g., open-label extensions of trials), and not yet recruiting. We do not comment on

RESEARCH IN CONTEXT

1. Systematic Review: We searched clinicaltrials.gov to identify all drugs currently being tested in Alzheimer's disease (AD) clinical trials. There are 143 agents being assessed in 172 trials. Most of the drugs being assessed are disease-modifying agents addressing a wide variety of biological processes involved in AD. We used artificial intelligence (AI) and machine learning (ML) to enhance our registry search techniques.
2. Interpretation: AD drug development is progressing despite temporary slowing of clinical trial activity during the COVID pandemic. The first disease-modifying therapy for AD (aducanumab) has been approved by the US Food and Drug Administration (FDA) and other disease-modifying therapies are advancing in clinical trials. There is progress in clinical trial outcome measures, biomarkers indicative of drug efficacy and safety, and clinical trial designs that provide the foundation for development of new and better therapies for patients with AD.
3. Future Directions: Improved understanding of the biology of AD and better approaches to drug discovery are providing improved candidates for clinical trials. Biomarkers are now used to confirm the presence of AD-type pathology in clinical trial participants. Biomarkers are playing a greater role as outcomes of disease-modifying therapy trials and amyloid plaque lowering on a biomarker (amyloid positron emission tomography) was the basis for accelerated approval of aducanumab. Improvements in drug candidates and trial methodologies increase confidence in the future development of new therapies for AD.

trials listed as terminated, suspended, unknown, or withdrawn unless the specific reasons for their status were publicly revealed. We do not include trials of non-pharmacologic therapeutic approaches such as cognitive-behavior therapies, caregiver interventions, supplements, medical foods, or devices. We do not include trials of biomarkers; we note whether biomarkers were used in the trials for inclusion or as outcome measures. We include stem cell therapies among the interventions reviewed (they are not integrated into Figure 1).

We use the National Institute on Aging and the Alzheimer's Association, International Alzheimer's and Related Dementias Research Portfolio (IADRP) approach to the MoA of agents in the pipeline (iadrp.nia.nih.gov). The IADRP catalogue of AD research is the Common Alzheimer's Disease Research Ontology (CADRO). The Translational Research and Clinical Interventions category of CADRO lists potential targets for AD and ADRD therapeutics from early therapeutic discovery through late-stage preclinical development and all stages of clinical testing. These targets were used to classify the MoA of the agents in the pipeline. The targets include amyloid; tau; apolipoprotein E (APOE)/lipids, and lipoprotein receptors; neurotransmitter receptors; neurogenesis; inflammation; oxidative stress; cell death; proteostasis/proteinopathies; metabolism and bioenergetics; vasculature; growth factors and hormones; synaptic plasticity/neuroprotection; gut-brain axis; circadian rhythm; epigenetic regulators; multi-target; unknown target, and other. Some agents may have more than one MoA and, for these we reviewed the available literature to identify the putative predominant mechanism. "Symptomatic" was used for treatments whose purpose was cognitive enhancement or control of neuropsychiatric symptoms without claiming to impact the underlying biological causes of AD. "Disease-modifying" was used for treatments intended to change the biology of AD and produce neuroprotection (often through a variety of intermediate mechanisms such as effects on amyloid or tau).[16] We used the features of the trials (e.g., clinical outcomes, trial duration, use of biomarkers, and number of participants) to determine whether a trial was attempting to demonstrate disease modification or symptomatic benefit. We recognize that these definitions are arbitrary, and many therapies may have symptomatic and disease-modifying effects. We divided DMTs into biologics (e.g., monoclonal antibodies, vaccines, antisense oligonucleotides [ASOs], and gene therapy) and small molecules (drugs typically taken orally and < 500 Daltons in molecular weight). We note if the trials are prevention studies of asymptomatic individuals or treatment trials of participants with MCI due to AD or AD dementia. Prevention trials include participants with normal cognition and biological evidence of AD pathology; trials of participants with prodromal AD comprise individuals manifesting MCI who have biomarker evidence indicative of AD pathology; and trials of AD dementia include participants with mild, moderate, or severe dementia.

We used AI and ML to facilitate our analyses. AI strategies were used to assist reading text and ML techniques were used to extract information automatically. We used supervised natural language processing classification approaches to categorize text describing a drug's MoA into two categories: small molecules and DMTs. We used term frequency-inverse document frequency (TF-IDF) to generate the words' matrix representation of the text and trained several ML models including XGBoost, random forest, logistic regression, decision tree, and support vector machine. The decision tree model achieved the highest accuracy (95%) in classifying the drugs' MoA texts.[17] Human supervision verified the results and solved any unresolved identifications. In addition to ML models, we used multiple pattern extraction methods to extract information regarding biomarkers and other trials features from the trial's text description.

To generate the tables and data used in the pipeline, we designed a sentinel system to collect the needed data automatically from clinicaltrials.gov and store it in a relational database system. In this system, charts and graphs can be generated to provide insight into the data and illustrate trends. The sentinel system automatically updates daily to capture any changes posted on clinicaltrials.gov of any relevant trial as defined by our search parameters. The system generates an e-mail notification as new data are identified and imported into the database.

FIGURE 1 Agents in clinical trials for treatment of Alzheimer's disease in 2021 (from clinicaltrials.gov as of the index date of January 5, 2021). The inner ring shows Phase 3 agents; the middle ring comprises Phase 2 agents; the outer ring presents Phase 1 therapies; agents in green areas are biologics; agents in purple are disease-modifying small molecules; agents in orange areas are symptomatic agents addressing cognitive enhancement or behavioral and neuropsychiatric symptoms; the shape of the icon shows the population of the trial; the icon color shows the Common Alzheimer's Disease Research Ontology (CADRO)-based class of the agent ("Other" category includes CADRO classes that have three or fewer agents in trials). Agents underlined are new to the pipeline since 2020. (Figure © J Cummings; M de la Flor, PhD, Illustrator)

3 | RESULTS

3.1 | Overview

We identified 143 agents in 172 trials of treatments for AD (as of the index date of January 25, 2022). There were 31 agents in 47 Phase 3 trials; 82 agents in 94 Phase 2 trials; and 30 agents in 31 Phase 1 trials. Figure 1 shows all pharmacologic compounds (biologics and small molecules) currently in clinical trials for AD. The most common agents being studied are DMTs (119 agents; 83.2% of the total number of agents in trials); 24 (16.8%) are symptomatic agents including 14 (9.8% of all agents in trials) targeting cognitive enhancement and 10 (6.9% of all agents in trials) intending to treat neuropsychiatric and behavioral symptoms. Of the DMTs, 40 (33.6% of DMTs) are biologics and 79 (66.4% of DMTs) are small molecules. Twenty (16.8%) DMTs have amyloid, 13 (10.9%) have tau, 23 (19.3%) have inflammation, and 19 (16%) have synaptic plasticity/neuroprotection as their primary mechanistic targets. Considering DMTs only, 21 (67.8%) of Phase 3 agents

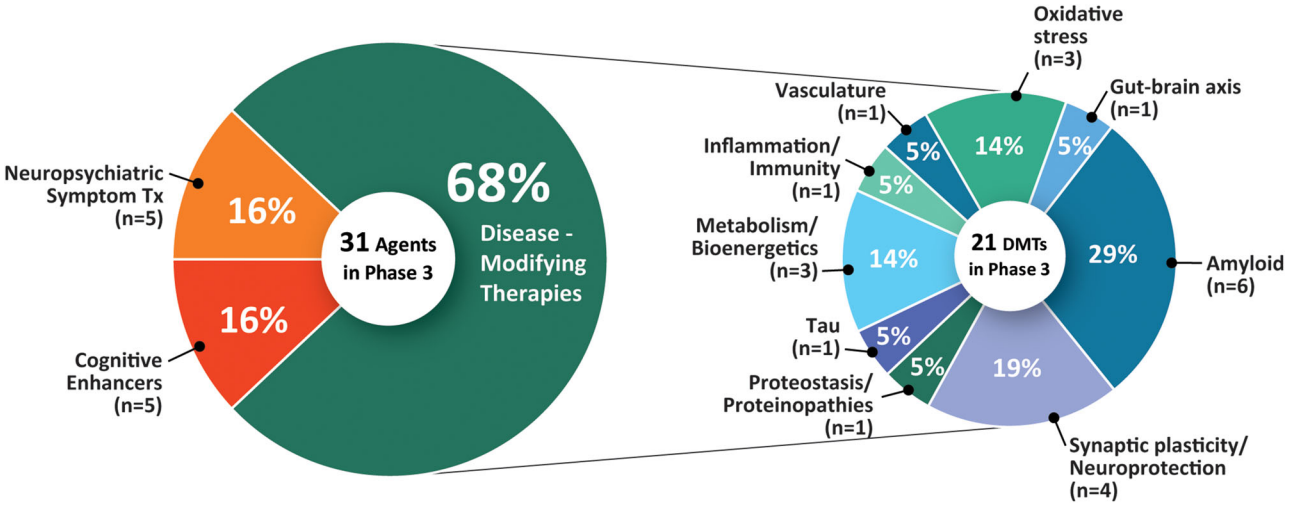

FIGURE 2 Mechanisms of action of agents in Phase 3 (as classified using the Common Alzheimer's Disease Research Ontology [CADRO] approach) (Figure © J Cummings; M de la Flor, PhD, Illustrator)

are DMTs; 71 (86.6%) Phase 2 drugs are DMTs; and 27 (90%) Phase 1 agents are DMTs. There are 53 repurposed agents in the pipeline comprising 37.1% of the candidate therapies (all phases combined).

3.2 | Phase 3

There are 31 agents in 47 Phase 3 trials (Figures 1 and 2, Table 1). Twenty-one (67.8%) agents in Phase 3 trials are DMTs including five (16.1% of the Phase 3 agents) biologics and 16 (51.6%) small molecules. There are five (16.1% of Phase 3 agents) putative cognitive enhancing agents and five (16.1%) drugs targeting behavioral symptoms. CADRO mechanisms represented among Phase 3 DMTs include amyloid (6 agents; 28.6% of DMTs); synaptic plasticity/neuroprotection (4; 19%); oxidative stress (3; 14.3%); metabolism and bioenergetics (3; 14.3%); tau (1; 4.8%); inflammation (1; 4.8%); proteostasis/proteinopathies (1; 4.8%); vasculature (1; 4.8%); and gut-brain axis (1; 4.8%). Figure 2 shows the CADRO-based MOAs of agents in Phase 3. Thirteen (42%) of the Phase 3 agent are repurposed treatments approved for use in another indication (8 = DMT; 2 = cognitive enhancer; 3 = treatment for neuropsychiatric symptoms). In the past year (2021), four trials have been completed or terminated.

Six of the trials in Phase 3 are prevention trials enrolling cognitively normal participants known to be at risk for AD (preclinical AD); one trial enrolling both preclinical participants and participants with MCI to mild AD dementia (DIAN-TU trial); 17 trials enrolling early AD defined as prodromal AD and mild AD dementia; 11 trials including participants with mild to moderate AD dementia; and 12 trials of participants with mild-to-severe AD dementia.

Trials in Phase 3 included a mean of 791 participants per trial (range 112 to 3300) and a total of 37,184 participants were needed for enrollment in all currently active Phase 3 trials. DMT prevention trials included a mean of 1058 participants (range 150 to 3300) and had a mean duration of 362 weeks (range 256 to 500 weeks, including the recruitment and the treatment period). DMT trials focusing on prodromal AD or prodromal AD/mild AD dementia had a mean of 991 participants (range 116 to 2032) and a mean duration of 243 weeks (range 83 to 500 weeks, including the recruitment and the treatment period). Trials of DMTs enrolling mild to moderate AD dementia participants included an average of 776 participants (range 316 to 2046) and a mean duration of 162 weeks (range 73 to 309 weeks, including the recruitment and the treatment period).

The mean treatment exposure period was 159 weeks (range 80 to 240 weeks) for prevention trials, 105 weeks (range 48 to 208 weeks) for prodromal AD or prodromal AD/mild AD dementia trials, and 48 weeks (range 20 to 76 weeks) for mild to moderate AD dementia trials. Calculated recruitment periods (calculated as the total projected time until the primary completion date minus the treatment period) for DMT trials were: prevention (183 weeks), prodromal AD and prodromal AD/mild AD dementia (93 weeks), and mild to moderate AD dementia (91 weeks).

The mean duration of cognitive enhancer trials was 167 weeks (range 130 to 208 weeks) including 24 treatment weeks (range 12 to 30 weeks), and they intended to recruit an average of 392 participants (range 160 to 712). The mean duration of trials of treatments for neuropsychiatric symptoms was 218 weeks (range 100 to 408 weeks) including 18 treatment weeks (range 8 to 52 weeks), and they included an average of 478 participants (range 112 to 1200).

3.3 | Phase 2

There are 82 agents in 94 Phase 2 trials (Figures 1 and 3, Table 2). Seventy-one (86.6%) of the agents in Phase 2 trials are DMTs including 26 (31.7% of the Phase 2 agents) biologics and 45 (54.8%) small molecules. There are seven (8.5% of Phase 2 agents) putative cognitive enhancing agents and four (4.9%) drugs targeting behavioral symptoms. CADRO mechanisms represented among Phase 2 DMT

TABLE 1 Agents in Phase 3 of Alzheimer's disease drug development (clinicaltrials.gov accessed January 25, 2022)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Aducanumab	Amyloid	Monoclonal antibody directed at Aβ plaques and oligomers	DMT	Active, not recruiting (NCT04241068)	Biogen	Mar 2020	Oct 2023
AGB101 (low-dose levetiracetam)	Synaptic Plasticity/Neuroprotection	SV2A modulator; to reduce Aβ-induced neuronal hyperactivity	DMT	Active, not recruiting[a] (NCT03486938)	AgeneBio, NIA	Jan 2019	Dec 2022
Atuzaginstat (COR388)	Synaptic Plasticity/Neuroprotection	Bacterial protease inhibitor targeting gingipain produced by *P. gingivalis* to reduce neuroinflammation and hippocampal degeneration	DMT	Active, not recruiting[a] (NCT03823404)	Cortexyme	Mar 2019	Dec 2022
AVP-786	Neurotransmitter receptors	Sigma 1 receptor agonist; NMDA receptor antagonist	Neuropsychiatric symptoms agent (agitation)	Recruiting (NCT03393520)	Avanir	Oct 2017	Jul 2022
				Recruiting, extension study (NCT02446132)	Avanir	Dec 2015	Oct 2023
				Recruiting (NCT04464564)	Avanir	Sep 2020	Dec 2024
				Recruiting, extension study (NCT04408755)	Avanir	Jul 2020	Dec 2024
AXS-05	Neurotransmitter receptors	NMDA receptor antagonist; combination of dextromethorphan and bupropion	Neuropsychiatric symptoms agent (agitation)	Recruiting (NCT04797715)	Axsome therapeutics	Dec 2020	Dec 2022
				Recruiting, extension study (NCT04947553)	Axsome therapeutics	Jun 2021	Jun 2023
Blarcamesine (ANAVEX2-73)	Synaptic plasticity/neuroprotection	Sigma-1 receptor agonist, M2 autoreceptor antagonist; to ameliorate oxidative stress, protein misfolding, mitochondrial dysfunction, and inflammation	DMT	Active, not recruiting[a] (NCT03790709)	Anavex life sciences	Jul 2018	Jun 2022
				Recruiting[a] (NCT04314934)	Anavex life sciences	Oct 2019	Jun 2024
BPDO-1603	Undisclosed	Undisclosed	Cognitive enhancer	Recruiting (NCT04229927)	Hyundai pharmaceutical	Feb 2020	Mar 2023

(Continues)

TABLE 1 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Brexpiprazole	Neurotransmitter receptors	Atypical antipsychotic; D2 receptor partial agonist; serotonin-dopamine modulator	Neuropsychiatric symptoms agent (agitation)	Recruiting[a] (NCT03620981)	Otsuka	Aug 2018	Aug 2022
				Recruiting, extension study (NCT03594123)	Otsuka	Oct 2018	Jul 2022
				Recruiting (NCT03548584)	Otsuka	May 2018	Apr 2022
Caffeine	Neurotransmitter receptors	Adenosine antagonist; non-specific phosphodiesterase inhibitor	Cognitive enhancer	Not yet recruiting (NCT04570085)	University Hospital, Lille	Nov 2021	Nov 2024
Donanemab	Amyloid	Monoclonal antibody specific for pyroglutamate form of Aβ	DMT	Active, not recruiting (NCT04437511)	Eli Lilly	Jun 2020	Aug 2025
				Recruiting (NCT05026866)	Eli Lilly	Aug 2021	Nov 2027
Donanemab & Aducanumab	Amyloid	Monoclonal antibody specific for pyroglutamate form of Aβ (donanemab); monoclonal antibody directed at plaques and oligomers (aducanumab); given in separate arms of the trial	DMT	Recruiting (NCT05108922)	Eli Lilly	Nov 2021	Jun 2023
Donepezil	Neurotransmitter receptors	Acetylcholinesterase inhibitor	Cognitive enhancer	Not yet recruiting (NCT04661280)	Assistance Publique – Hôpitaux de Paris	Jan 2022	Jul 2024
Escitalopram	Neurotransmitter receptors	Selective serotonin reuptake inhibitor	Neuropsychiatric symptoms agent (agitation)	Recruiting (NCT03108846)	Johns Hopkins University, NIA	Jan 2018	Aug 2022
Gantenerumab	Amyloid	Monoclonal antibody directed at Aβ plaques and oligomers	DMT	Recruiting (NCT03444870)	Roche	Jun 2018	Oct 2026
				Active, not recruiting (NCT03443973)	Roche	Aug 2018	Aug 2023
				Active, not recruiting, extension study; (NCT04339413)	Roche	May 2020	Apr 2023
				Recruiting, extension study; (NCT04374253)	Roche	Feb 2021	Dec 2024

(Continues)

TABLE 1 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Gantenerumab & Solanezumab	Amyloid	Monoclonal antibody directed at Aβ plaques and oligomers (gantenerumab); Monoclonal antibody directed at Aβ monomers (solanezumab); given in separate arms of the trial	DMT	Recruiting[a]; (NCT01760005)	Washington University, Eli Lilly, Roche, NIA, Alzheimer's Association	Dec 2012	Jul 2022
Guanfacine	Neurotransmitter receptors	Alpha-2 adrenergic agonist	Cognitive enhancer	Recruiting; (NCT03116126)	Imperial College London, UK National Institute of Health Research	Jan 2019	Dec 2022
GV-971	Gut-brain axis	Algae-derived acidic oligosaccharides; changes microbiome to reduce peripheral and central inflammation	DMT	Recruiting; (NCT04520412)	Shanghai Greenvalley	Oct 2020	Oct 2026
Hydralazine	Oxidative stress	Free radical scavenger	DMT	Recruiting; (NCT04842552)	Shahid Sadoughi University, Iran	Jun 2021	Dec 2023
Icosapent ethyl (IPE)	Oxidative stress	Purified form of the omega-3 fatty acid EPA; to improve synaptic function and reduce inflammation	DMT	Active, not recruiting[a]; (NCT02719327)	VA Office of Research and Development, University of Wisconsin, Madison	Jun 2017	Jan 2023
Lecanemab (BAN2401)	Amyloid	Monoclonal antibody directed at Aβ protofibrils	DMT	Active, not recruiting; (NCT03887455)	Eisai, Biogen	Mar 2019	Aug 2024
				Recruiting; (NCT04468659)	Eisai, Biogen, ACTC, NIA	Jul 2020	Oct 2027
Losartan & Amlodipine & Atorvastatin + exercise	Vasculature	Angiotensin II receptor blocker (losartan), calcium channel blocker (amlodipine), cholesterol agent (atorvastatin)	DMT	Active, not recruiting[a]; (NCT02913664)	University of Texas Southwestern	Feb 2017	Jan 2022
Metformin	Metabolism and bioenergetics	Insulin sensitizer to improve CNS glucose metabolism	DMT	Recruiting[a]; (NCT04098666)	Columbia University, NIA	Apr 2021	Apr 2025
Nabilone	Neurotransmitter receptors	Synthetic cannabinoid	Neuropsychiatric symptoms agent (agitation)	Recruiting (NCT04516057)	Sunnybrook Health Sciences Center, ADDF	Feb 2021	Oct 2025
NE3107	Inflammation	MAPK-1/3 inhibitor; reduces proinflammatory NFκB activation	DMT	Recruiting; (NCT04669028)	Neurmedix	Aug 2021	Jan 2023

(Continues)

TABLE 1 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Nilotinib BE	Proteostasis/ Proteinopathies	Tyrosine kinase inhibitor; autophagy enhancer; promotes clearance of Aβ and tau	DMT	Not yet recruiting; (NCT05143528)	KeifeRx	Feb 2022	Jun 2026
Octohydro-aminoacridine Succinate	Neurotransmitter receptors	Acetylcholinesterase inhibitor	Cognitive enhancer	Recruiting; (NCT03283059)	Shanghai Mental Health Center	Aug 2017	Feb 2021
Omega-3 (DHA+EPA)	Oxidative stress	Antioxidant	DMT	Recruiting; (NCT03691519)	University Hospital, Toulouse	Apr 2018	Dec 2023
Semaglutide	Metabolism and bioenergetics	GLP-1 agonist; reduces neuroinflammation and improves insulin signaling in the brain	DMT	Recruiting; (NCT04777396)	Novo Nordisk	May 2021	Apr 2026
				Recruiting; (NCT04777409)	Novo Nordisk	May 2021	Apr 2026
Simufilam (PTI-125)	Synaptic Plastic-ity/Neuroprotection	Filamin A protein inhibitor; stabilizes amyloid-alpha-7 nicotinic receptor interaction	DMT	Recruiting; (NCT04994483)	Cassava sciences	Nov 2021	Oct 2023
				Recruiting; (NCT05026177)	Cassava sciences	Dec 2021	Jun 2024
Solanezumab	Amyloid	Monoclonal antibody directed at Aβ monomers	DMT	Active, not recruiting; (NCT02008357)	Eli Lilly, ATRI	Feb 2014	Jun 2023
Tricaprilin	Metabolism and bioenergetics	Caprylic triglyceride; induces ketosis and improves mitochondrial and neuronal function	DMT	Not yet recruiting; (NCT04187547)	Cerecin	Jun 2022	Feb 2024
TRx0237	Tau	Tau protein aggregation inhibitor	DMT	Active, not recruiting; (NCT03446001)	TauRx Therapeutics	Jan 2018	Mar 2023
Valiltramiprosate (ALZ-801)	Amyloid	Prodrug of tramiprosate; inhibits Aβ aggregation into toxic oligomers	DMT	Recruiting; (NCT04770220)	Alzheon, NIA	May 2021	May 2024

NOTE. Thirty-one agents in 47 Phase 3 clinical trials currently ongoing as of January 25, 2022 according to clinicaltrials.gov.

Abbreviations: Aβ, amyloid beta; ACTC, Alzheimer's Clinical Trial Consortium; ADDF, Alzheimer's Drug Discovery Foundation; ATRI, Alzheimer's Therapeutic Research Institute; BE, bioequivalent; CADRO, Common Alzheimer's Disease and Related Disorders Research Ontology; DMT, disease-modifying therapy; EPA, eicosapentaenoic acid; GLP-1, glucagon-like peptide-1; MAPK, mitogen activated protein kinase; NFκB, Nuclear Factor Kappa B; NIA, National Institute on Aging; NMDA, N-methyl-D-aspartate; SV2A, synaptic vesicle protein 2A.

[a] Phase 2/3 trials.

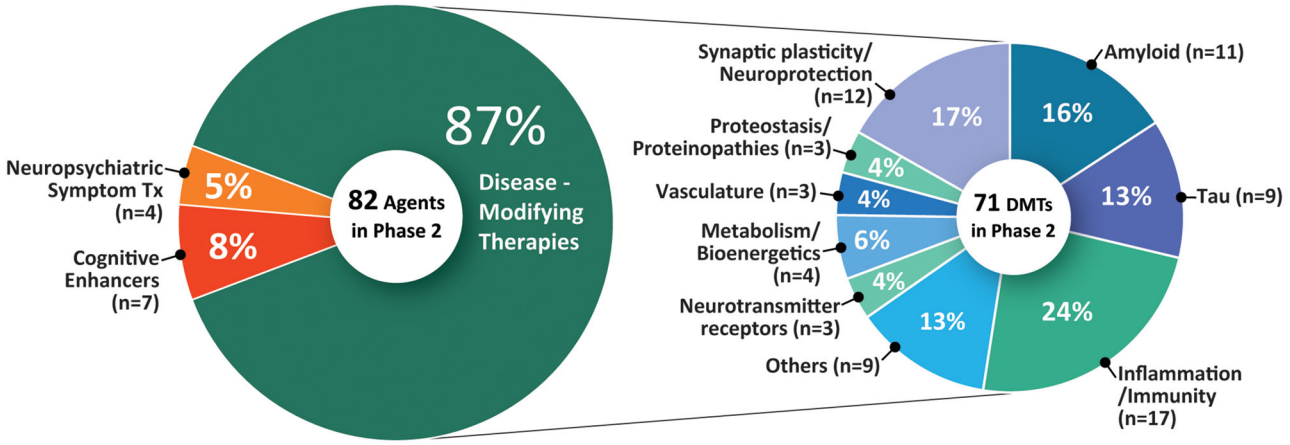

FIGURE 3 Mechanisms of action of agents in Phase 2 (Figure © J Cummings; M de la Flor, PhD, Illustrator)

therapies include inflammation (17 agents; 24% of DMTs); synaptic plasticity/neuroprotection (12; 16.9%); amyloid (11; 15.5%); tau (9; 12.7%); metabolism and bioenergetics (4; 5.6%); neurotransmitter receptors (3; 4.2%); proteostasis/proteinopathies (3; 4.2%); vasculature (3; 4.2%); neurogenesis (2; 2.8%); growth factors and hormones (2; 2.8%); epigenetic regulators (2; 2.8%); ApoE, lipids, and lipoprotein receptors (1; 1.4%); oxidative stress (1; 1.4%); and cell death (1; 1.4%). Figure 3 shows the CADRO-based MoAs of agents in Phase 2. Thirty-one (37.8%) of the Phase 2 agents are repurposed from another indication (27 = DMT; 1 = cognitive enhancer; 3 = treatment for neuropsychiatric symptoms). In the past year (2021), 23 Phase 2 trials have been completed or terminated.

There are five trials in Phase 2 involving cell therapies (Table 3).

Four (4%) of the trials in Phase 2 are prevention trials enrolling cognitively normal participants known to be at risk for AD (preclinical AD); three (3%) trials enroll both preclinical participants and participants with MCI to mild AD dementia; 49 (52%) trials enroll early AD defined as prodromal AD and mild AD dementia; 34 (36%) trials are with participants with mild to moderate AD dementia; two (2%) trials include participants with mild-to-severe AD dementia; and two (2%) trials enroll healthy volunteers.

Trials in Phase 2 included a mean of 127 participants per trial (range 5 to 856) and a total of 11,938 participants were needed for enrollment in all currently active Phase 2 trials. DMT prevention trials included a mean of 151 participants (range 32 to 320) and had a mean duration of 284 weeks (range 155 to 471 weeks, including the recruitment and the treatment period). DMT trials focusing on prodromal AD or prodromal AD/mild AD dementia had a mean of 138 participants (range 5 to 856) and a mean duration of 198 weeks (range 40 to 635 weeks, including the recruitment and the treatment period). Trials of DMTs enrolling mild to moderate AD dementia participants included an average of 107 participants (range 8 to 350) and a mean duration of 172 weeks (range 70 to 417 weeks, including the recruitment and the treatment period).

The mean treatment exposure period was 97 weeks (range 3 to 260 weeks) for prevention trials, 53 weeks (range 3 to 260 weeks) for prodromal AD or prodromal AD/mild AD dementia trials, and 31 weeks (range 8 to 108 weeks) for mild to moderate AD dementia trials. Recruitment periods (calculated as the total projected time until the primary completion date minus the treatment period) for DMT trials were prevention (145 weeks), prodromal AD and prodromal AD/mild AD dementia (117 weeks), and mild to moderate AD dementia (118 weeks).

The mean duration of Phase 2 cognitive enhancer trials was 127 weeks (range 39 to 337 weeks) including 27 treatment weeks (range 2 to 104 weeks), and they included an average of 105 participants (range 28 to 300). The mean duration of Phase 2 trials of treatments for neuropsychiatric symptoms was 150 weeks (range 39 to 321 weeks) including eight treatment weeks (range 1 to 15 weeks), and they included an average of 122 participants (range 40 to 186).

3.4 | Phase 1

There are 30 agents in 31 Phase 1 trials (Figure 1, Table 4). There are 27 DMTs (90% of Phase 1 agents) in Phase 1 trials including nine (30% of the Phase 1 agents) biologics and 18 (60%) small molecules. There are two (6.7% of Phase 1 agents) putative cognitive enhancing agents and one (3.3%) drug intended to target behavioral symptoms. CADRO mechanisms represented among Phase 1 DMT therapies include inflammation (5 agents; 18.5% of DMTs); epigenetic regulators (4; 14.8%); amyloid (3; 11.1%); tau (3; 11.1%); proteostasis/proteinopathies (3; 11.1%); synaptic plasticity/neuroprotection (3; 11.1%); neurogenesis (2; 7.4%); vasculature (2; 7.4%); cell death (1; 3.7%); and metabolism and bioenergetics (1; 3.7%). Nine (30%) of the Phase 1 agents are repurposed treatments approved for use in another indication (eight DMTs; one cognitive enhancer). There are two trials in Phase 1 involving stem cell therapies.

Phase 1 trials have an average duration of 115 weeks (range 24 to 365 weeks) (recruitment and treatment period) and include a mean of 47 participants (range 5 to 120) in each trial. Phase 1 trials include both single ascending dose and multiple ascending dose studies.

TABLE 2 Agents in Phase 2 of Alzheimer's disease drug development (clinicaltrials.gov accessed January 25, 2022)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
ABvac40	Amyloid	Active immunotherapy to remove Aβ	DMT	Active, not recruiting; (NCT03461276)	Araclon Biotech	Feb 2018	Dec 2022
ACI-35	Tau	Active immunotherapy targeting tau	DMT	Recruiting[a]; (NCT04445831)	AC Immune, Janssen	Jul 2019	Oct 2023
AD-35	Neurotransmitter receptors	Acetylcholinesterase inhibitor	Cognitive enhancer	Active, not recruiting; (NCT03625401)	Zhejiang Hisun Pharmaceutical	Oct 2018	Dec 2020
AL002	Inflammation	Monoclonal antibody targeting TREM2 receptors to promote microglial clearance of Aβ	DMT	Recruiting; (NCT04592874)	Alector, AbbVie	Jan 2021	Aug 2023
Allopregnanolone	Neurogenesis	Allosteric modulator of GABA-A receptors	DMT	Not yet recruiting; (NCT04838301)	University of Arizona, NIA	Nov 2021	Jun 2024
APH-1105	Amyloid	Alpha-secretase modulator to reduce Aβ production	DMT	Not yet recruiting; (NCT03806478)	Aphios	Jun 2023	Dec 2024
Baricitinib	Inflammation	Janus kinase inhibitor; reduces neuroinflammation	DMT	Not yet recruiting[a]; (NCT05189106)	Massachusetts General Hospital	Feb 2022	Oct 2023
Bepranemab	Tau	Anti-tau monoclonal antibody	DMT	Recruiting; (NCT04867616)	UCB Biopharma	Jun 2021	Nov 2025
BCG vaccine	Inflammation/ Immunity	Immunomodulator	DMT	Not yet recruiting; (NCT05004688)	Massachusetts General Hospital	Dec 2021	Oct 2023
BPN14770	Synaptic plasticity/neuroprotection	PDE-4 inhibitor; prolongs cAMP activity and improves neuronal plasticity	DMT	Active, not recruiting; (NCT03817684)	Tetra discovery partners	Apr 2019	Feb 2020
Bromocriptine	Neurotransmitter receptors	Dopamine agonist with anti-Aβ effects	DMT	Active, not recruiting[a]; (NCT04413344)	Kyoto University	Jun 2020	Mar 2022
Bryostatin 1	Synaptic plasticity/neuroprotection	Protein Kinase C inhibitor; facilitates synaptogenesis	DMT	Recruiting; (NCT04538066)	Neurotrope Bioscience, NIH, NIA	Aug 2020	Nov 2022
BXCL-501	Neurotransmitter receptors	Sublingual dexmedetomidine; selective α2-adrenergic receptor agonist	Neuropsychiatric symptoms agent (agitation)	Recruiting; (NCT04251910)	BioXcel therapeutics	Dec 2020	Sep 2021
Canakinumab	Inflammation	Anti-IL-1β monoclonal antibody	DMT	Recruiting; (NCT04795466)	Novartis	Oct 2021	Jan 2024
CORT108297	Hormones	Selective glucocorticoid receptor antagonist; reduce neuroendocrine stress responses	Cognitive enhancer	Recruiting; (NCT04601038)	Johns Hopkins University	Jun 2021	Jan 2024
Crenezumab	Amyloid	Monoclonal antibody targeting soluble Aβ oligomers	DMT	Active, not recruiting; (NCT01998841)	Genentech, NIA Banner Alzheimer's Institute	Dec 2013	Dec 2022
CST-2032	Neurotransmitter receptors	Noradrenergic agonist	Cognitive enhancer	Not yet recruiting; (NCT05104463)	CuraSen Therapeutics	Jan 2022	Oct 2022

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Curcumin + aerobic yoga	Inflammation	Herb with antioxidant and anti-inflammatory properties	DMT	Active, not recruiting; (NCT01811381)	VA Office of Research and Development	Jan 2014	Dec 2020
CY6463	Synaptic Plasticity/Neuroprotection	Guanylate cyclase positive allosteric modulator	DMT	Recruiting; (NCT04798989)	Cyclerion therapeutics	Jun 2021	Jul 2022
DAOIB	Neurotransmitter receptors	NMDA receptor antagonist to augment the effect of tDCS	Cognitive enhancer	NCT05006781	Chang Gung Memorial Hospital	Mar 2022	Aug 2025
Dapagliflozin	Metabolism and bioenergetics	SGLT2 inhibitor; to improve insulin sensitivity and CNS glucose metabolism	DMT	Recruiting[a]; (NCT03801642)	University of Kansas	Jan 2019	Oct 2022
Daratumumab	Inflammation/ immunity	Monoclonal antibody targeting CD38; regulates microglial activity	DMT	Recruiting; (NCT04070378)	Northwell Health, Janssen	Nov 2019	Jun 2023
Dasatinib + Quercetin	Inflammation/ immunity	Tyrosine kinase inhibitor (dasatinib) and flavonoid (quercetin); senolytic therapy approach to reduce senescent cells and tau aggregation	DMT	Recruiting[a]; (NCT04063124)	The University of Texas at San Antonio, Mayo Clinic	Feb 2020	Aug 2023
				Recruiting; (NCT04685590)	Wake Forest University, The University of Texas at San Antonio	Jan 2022	Jan 2032
				Recruiting[a]; (NCT04785300)	Mayo Clinic	Oct 2021	Jun 2023
Deferiprone	Cell death	Iron chelating agent; reduce damaging reactive oxygen species	DMT	Active, not recruiting; (NCT03234686)	Neuroscience Trials Australia	Jan 2018	Sep 2023
DHA	Oxidative stress	Omega 3 fatty acid; improve synaptic function; antioxidant	DMT	Recruiting; (NCT03613844)	University of Southern California, NIA, ADDF	Jul 2018	Dec 2024
Donanemab (LY3002813)	Amyloid	Monoclonal antibody specific for pyroglutamate Aβ	DMT	Active, not recruiting; (NCT03367403)	Eli Lilly	Dec 2017	Nov 2021
				Recruiting; (NCT04640077)	Eli Lilly	Nov 2020	Oct 2023
Dronabinol	Neurotransmitter receptors	CB1 and CB2 endocannabinoid receptor partial agonist	Neuropsychiatric symptoms agent (agitation)	Recruiting; (NCT02792257)	Mclean Hospital, Johns Hopkins University	Mar 2017	May 2023
E2814	Tau	Anti-tau monoclonal antibody	DMT	Recruiting[a]; (NCT04971733)	Eisai	Jun 2021	Apr 2024
Edonerpic (T-817MA)	Synaptic plasticity/neuroprotection	Neurotrophic agent; activates sigma receptors to preserve synaptic plasticity; protect against Aβ toxicity	DMT	Active, not recruiting; (NCT04191486)	Toyama Chemical	Dec 2019	Mar 2023
Elayta (CT1812)	Synaptic plasticity/ neuroprotection	Sigma-2 receptor antagonist; competes with oligomeric Aβ binding; protect against Aβ-induced synaptic toxicity	DMT	Recruiting; (NCT03507790)	Cognition therapeutics	Oct 2018	Oct 2023
				Recruiting; (NCT04735536)	Cognition therapeutics	Jul 2020	Jul 2022

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
ExPlas (exercised plasma)	Synaptic plasticity/neuroprotection	Plasma transfusion from exercise-trained donors	DMT	Recruiting; (NCT05068830)	Norwegian University, St. Olavs Hospital	Sep 2021	Sep 2025
Fosgonimeton (ATH-1017)	Synaptic plasticity/neuroprote	Activates signaling via the hepatocyte growth factor system to regenerate neurons and enhance synaptic plasticity	DMT	Recruiting; (NCT04488419)	Athira Pharma	Sep 2020	Oct 2022
				Active, not recruiting; (NCT04491006)	Athira Pharma	Nov 2020	May 2022
				Recruiting, extension study; (NCT04886063)	Athira Pharma	Jun 2021	May 2023
Gantenerumab	Amyloid	Monoclonal antibody directed at Aβ plaques and oligomers	DMT	Active, not recruiting; (NCT04592341)	Roche	Nov 2020	Nov 2023
Brain Shuttle Gantenerumab (RO7126209)	Amyloid	Anti-Aβ monoclonal antibody (gantenerumab) with enhanced blood-brain barrier penetration	DMT	Recruiting[a]; (NCT04639050)	Roche	Mar 2021	Oct 2024
GB301	Inflammation/ immunity	Regulatory T cells; reduce neuroinflammation	DMT	Not yet recruiting[a]; (NCT03865017)	GMP BIO, BHT Lifescience Australia	Dec 2019	Dec 2021
Grapeseed extract	Proteostasis/protein	Polyphenolic compound; antioxidant; prevent aggregation of Aβ and tau	DMT	Active, not recruiting; (NCT02033941)	Mount Sinai School of Medicine, NCCIH	Nov 2014	Dec 2021
GV1001	Epigenetic	hTERT peptide vaccine; mimics extra-telomeric functions to inhibit neurotoxicity, apoptosis, and reactive oxygen species	DMT	Not yet recruiting; (NCT03959553)	GemVax & Kael	Sep 2019	Feb 2022
				Not yet recruiting; (NCT05189210)	GemVax & Kael	May 2022	Sep 2024
Intranasal insulin	Metabolism and bioenergetics	Decrease glucose resistance and increase insulin signaling in the brain	DMT	Not yet recruiting; (NCT05006599)	Wake Forest University	Oct 2021	Oct 2025
Intranasal insulin + Empagliflozin	Metabolism and bioenergetics	SGLT2 inhibitor (empagliflozin) and insulin combination therapy; decrease glucose resistance and increase insulin signaling in the brain	DMT	Not yet recruiting; (NCT05081219)	Wake Forest University	Nov 2021	Nov 2028
IONIS MAPTRx (BIIB080)	Tau	Antisense oligonucleotide targeting tau expression; MAPT RNA inhibitor	DMT	Active, not recruiting[a]; (NCT03186989)	Ionis Pharmaceuticals	Jun 2017	May 2022
JNJ-63733657	Tau	Monoclonal antibody targeting soluble tau	DMT	Recruiting; (NCT04619420)	Janssen	Jan 2021	Nov 2025
Lamivudine (3TC)	Epigenetic	Nucleoside reverse transcriptase inhibitor; reduces genetic rearrangements	DMT	Recruiting[a]; (NCT04552795)	University of Texas Health Science Center at San Antonio	Feb 2021	Jun 2022
Lecanemab (BAN2401)	Amyloid	Monoclonal antibody directed at protofibrils	DMT	Active, not recruiting; (NCT01767311)	Eisai	Dec 2012	Feb 2025

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Lenalidomide	Inflammation/ immunity	Reduce inflammatory cytokines; modulate innate and adaptive immune responses	DMT	Recruiting; (NCT04032626)	Cleveland Clinic, NIA	Jul 2020	Sep 2024
Levetiracetam	Synaptic plasticity/ neuroprotection	SV2A modulator; improve synaptic function; reduce Aβ-induced neuronal hyperactivity	DMT	Active, not recruiting; (NCT02002819)	University of California, San Francisco	Jun 2014	Dec 2021
				Active, not recruiting; (NCT03489044)	UCB Pharma, University of Oxford, NHS Foundation Trust	Oct 2018	Dec 2022
				Recruiting; (NCT03875638)	Beth Israel Deaconess Medical Center	Aug 2019	Nov 2023
L-Serine	Inflammation	Dietary amino acid; reduce brain inflammation and preserve nerve cells	DMT	Active, not recruiting; (NCT03062449)	Dartmouth-Hitchcock Medical Center	Mar 2017	Dec 2022
Lupron (leuprolide acetate depot)	Growth factors and hormones	GnRH receptor agonist; reduce effects of elevated GnRH and gonadotropins on the brain	DMT	Recruiting; (NCT03649724)	New York University	Nov 2020	Feb 2026
LY3372689	Tau	O-GlycNAcase inhibitor; promote tau glycosylation, prevent tau aggregation	DMT	Recruiting; (NCT05063539)	Eli Lilly	Sep 2021	Jun 2024
Memantine	Neurotransmitter receptors	NMDA receptor antagonist	DMT	Recruiting; (NCT05063851)	University of Virginia	Oct 2021	Oct 2024
Metabolic cofactor supplementation	Metabolism and bioenergetics	Mixture of N-acetylcysteine, L-carnitine tartrate, nicotinamide roboside, and serine to increase mitochondrial activity	Cognitive enhancer	Recruiting; (NCT04044131)	Istanbul Medipol University Hospital, ScandiBio therapeutics	Dec 2019	Sep 2020
MIB-626	Amyloid	Sirtuin-nicotinamide adenine dinucleotide stimulator to enhance alpha-secretase	DMT	Not yet recruiting[a]; (NCT05040321)	Brigham and Women's Hospital	Dec 2021	Dec 2024
Montelukast	Inflammation	Cysteinyl leukotriene type 1 (cysLT-1) receptor antagonist; effects on inflammatory processes, neuronal injury, blood-brain-barrier integrity, and Aβ protein accumulation	DMT	Recruiting; (NCT03402503) –buccal film	IntelGenx Corp.	Nov 2018	Jul 2021
				Active, not recruiting; (NCT03991988) – tablet	Emory University	Sep 2019	Oct 2022
MW150	Synaptic plasticity/neuroprotection	p38 MAPK-α inhibitor	DMT	Not yet recruiting; (NCT05194163)	Neurokine Therapeutics, Columbia University, NIA	Feb 2022	Jan 2025
Neflamapimod (VX-745)	Synaptic plasticity/neuroprotection	p38 MAPK-α inhibitor; enhance endolysosomal function to reduce synaptic dysfunction	DMT	Recruiting; (NCT03435861)	EIP Pharma	Oct 2018	Jun 2021
Nicotinamide	Tau	HDAC inhibitor; to reduce tau-induced microtubule depolymerization and tau phosphorylation	DMT	Recruiting; (NCT03061474)	University of California, Irvine	Jul 2017	Jul 2022

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Nicotine transdermal patch	Neurotransmitter receptors	Nicotinic acetylcholine receptor agonist	Cognitive enhancer	Recruiting; (NCT02720445)	University of Southern California, NIA, ATRI, Vanderbilt University	Jan 2017	Jul 2023
Obicetrapib	Lipids and lipoprotein receptors	Cholesteryl ester transfer protein (CETP) inhibitor	DMT	Not yet recruitin; (NCT05161715)	NewAmsterdam Pharma	Dec 2021	Mar 2023
Omega-3 PUFA	Vasculature	Polyunsaturated fatty acid; reduce damage to small blood vessels	DMT	Active, not recruiting; (NCT01953705)	Oregon Health and Science University, NIA	May 2014	Jun 2021
Pepinemab (VX15)	Inflammation	Monoclonal antibody directed at semaphorin 4D to reduce inflammation	DMT	Recruiting[a]; (NCT04381468)	Vaccinex, ADDF, Alzheimer's Association	Jul 2021	Jan 2023
Posiphen	Proteostasis/ proteinopathies	Inhibitor of APP and α-synuclein	DMT	Active, not recruiting[a]; (NCT02925650)	QR Pharma, ADCS	Mar 2017	Feb 2022
				Active, not recruiting[a]; (NCT04524351)	Annovis Bio, Parexel	Aug 2020	Mar 2022
Prazosin	Neurotransmitter receptors	Alpha-1 adrenoreceptor antagonist	Neuropsychiatric symptoms agent (agitation)	Active, not recruiting; (NCT03710642)	ADCS, NIA	Oct 2018	Feb 2022
PU-AD	Tau	Heat shock protein 90 inhibitor; to prevent aggregation and hyperphosphorylation of tau	DMT	Active, not recruiting; (NCT04311515)	Samus therapeutics	Jun 2020	Dec 2022
Rapamycin (sirolimus)	Proteostasis/ proteinopathies	mTOR inhibitor; ameliorate metabolic and vascular effects of aging	DMT	Recruiting; (NCT04629495)	The University of Texas Health Science Center at San Antonio	Aug 2021	Aug 2024
Sargramostim	Inflammation/ immunity	Granulocyte macrophage colony stimulating factor	DMT	Not yet recruiting; (NCT04902703)	University of Colorado, NIA, Alzheimer's association, partner therapeutics	Dec 2021	Jul 2024
Semorinemab (RO7105705)	Tau	Monoclonal antibody to remove extracellular tau	DMT	Active, not recruiting; (NCT03828747)	Genentech	Jan 2019	Jun 2023
Senicapoc	Inflammation	Calcium-activated potassium channel blocker	DMT	Not yet recruiting; (NCT04804241)	University of California, Davis	Jan 2022	Jun 2023
Sovateltide (PMZ-1620)	Neurogenesis	Endothelin B receptor agonist; augments activity of neuronal progenitor cells	DMT	Recruiting; (NCT04052737)	Pharmazz	Mar 2018	Oct 2022
Simufilam (PTI-125)	Synaptic plasticity/neuroprotection	Filamin A protein inhibitor; stabilizes the interaction of soluble Aβ and the alpha7 nicotinic acetylcholine receptor, reducing Aβ and synaptic dysfunction	DMT	Active, not recruiting; (NCT04388254)	Cassava Sciences, NIA	Mar 2020	Jul 2023

(Continues)

TABLE 2 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Suvorexant	Neurotransmitter receptors	Dual Orexin receptor antagonist; improved sleep with effects on CSF Aβ	DMT	Not yet recruiting; (NCT04629547)	Washington University School of Medicine	Nov 2021	Jan 2025
T3D-959	Metabolism and bioenergetics	Dual agonist of PPARδ/γ; reduce glucose and lipid metabolism	DMT	Recruiting; (NCT04251182)	T3D Therapeutics, Alzheimer's Association, NIA	Mar 2021	Jul 2022
TB006	Inflammation	Monoclonal antibody targeting galactin 3	DMT	Recruiting[a]; (NCT05074498)	TrueBinding, Inc.	Oct 2021	Oct 2022
Telmisartan & perindopril	Vasculature	Angiotensin II receptor blocker (telmisartan); angiotensin converting enzyme inhibitor (perindopril)	DMT	Recruiting; (NCT02085265)	Sunnybrook Health Sciences Centre, ADDF	Mar 2014	Mar 2022
Tdap vaccine	Inflammation and immunity	Immune reaction to diphtheria, pertussis, tetanus vaccine	DMT	Not yet recruiting[a]; (NCT05183516)	Mindful diagnostics and therapeutics	May 2022	Mar 2023
THC-free CBD oil	Neurotransmitter receptors	Cannabinoid with effects on cannabinoid receptors	Neuropsychiatric symptoms agent (agitation)	Recruiting; (NCT04436081)	Eastern Virginia Medical School, Ananda Hemp	Feb 2021	Jun 2022
Thiethylperazine (TEP)	Amyloid	Activates transport protein ABCC1 to remove Aβ	DMT	Active, not recruiting; (NCT03417986)	Immungenetics AG	Nov 2017	Dec 2021
Troriluzole (BHV4157)	Synaptic plasticity/neuroprotection	Glutamate modulator; prodrug of riluzole; improve synaptic function	DMT	Active, not recruiting; (NCT03605667)	Biohaven Pharma, ADCS	Jul 2018	Jan 2022
Valacyclovir	Infection/immunity	Antiviral against HSV-1 and -2 infection; to prevent Aβ aggregation and plaque deposition	DMT	Recruiting; (NCT03282916)	New York State Psychiatric Institute, NIH, NIA	Feb 2018	Dec 2023
Valiltramiprosate (ALZ-801)	Amyloid	Prodrug of tramiprosate; inhibits Aβ aggregation into toxic oligomers	DMT	Active, note recruiting; (NCT04693520)	Alzheon	Sep 2020	Aug 2023
Varoglutamstat (PQ912)	Amyloid	Glutaminyl cyclase (QC) enzyme inhibitor to reduce pyroglutamate Aβ production	DMT	Recruiting; (NCT03919162)	Vivoryon Therapeutics AG, ADCS, NIA	Nov 2021	May 2023
				Recruiting; (NCT04498650)	Vivoryon Therapeutics AG, ADCS, NIA	Jul 2020	Jul 2023
VGH-AD1	Undisclosed	Traditional Chinese herbal medicine	Cognitive enhancer	Not yet recruiting; (NCT04249869)[a]	Taipei Veterans General Hospital, Taiwan	Feb 2020	Dec 2020
Xanamem	Growth factors and hormones	11-beta-hydroxysteroid dehydrogenase type 1 inhibitor	DMT	Active, not recruiting[a](NCT04983368)	Actinogen Medical	Jun 2021	Jun 2022
Yangxue Qingnao pills	Vasculature	Cerebral blood flow enhancer	DMT	Recruiting(NCT04780399)	Dongzhimen Hospital, Beijing	Nov 2021	Dec 2024

NOTE. Eighty-two agents in 94 Phase 2 clinical trials currently ongoing as of January 25, 2022 according to clinicaltrials.gov.

Abbreviations: Aβ, amyloid beta; ADCS, Alzheimer's Disease Cooperative Study; ADDF, Alzheimer's Drug Discovery Foundation; APP, amyloid precursor protein; CADRO, Common Alzheimer's Disease and Related Disorders Research Ontology; cAMP, cycling adenosine monophosphate; CB, cannabinoid; DMT, disease-modifying therapy; GnRH, gonadotropin-releasing hormone; HSV, herpes simplex virus; hTERT, human telomerase reverse transcriptase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NCCIH, National Center for Complementary and Integrative Health; NIA, National Institute on Aging; NMDA, N-methyl-D-aspartate; PDE, phosphodiesterase; PPARδ/γ, peroxisome proliferator nuclear receptor δ/γ; PUFA, polyunsaturated fatty acids; SGLT2, sodium glucose transporter 2; SV2A, synaptic vesicle protein 2A; tDCS, transcranial direct current stimulation; TREM2, Triggering Receptor Expressed On Myeloid Cells 2.

[a] Phase 1/2 trials.

TABLE 3 Agents in Phase 1 of Alzheimer's disease drug development (clinicaltrials.gov accessed January 25, 2022)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
AAV-Htert	Epigenetic	Extending telomeres may benefit AD; reduce Aβ-induced neurotoxicity; effects on multiple cellular pathways	DMT	Recruiting; (NCT04133454)	Libella Gene Therapeutics	Oct 2019	Jan 2021
ACU193	Amyloid	Monoclonal antibody targeting soluble Aβ	DMT	Recruiting; (NCT04931459)	Acumen Pharmaceuticals, NIA	Jun 2021	Dec 2022
Allopregnanolone	Neurogenesis	GABA-A receptor modulator; promote neurogenesis and reduce inflammation	DMT	Active, not recruiting; (NCT03748303)	University of Southern California, University of Arizona, Alzheimer's Association	Oct 2019	Oct 2022
ASN51	Tau	O-GlycNAcase Inhibitor	DMT	Recruiting; (NCT04759365)	Asceneuron	Jun 2021	Jan 2022
BEY2153	Proteostasis/ proteinopathies	Aβ and tau aggregation inhibitor; inhibits neuronal death	DMT	Recruiting; (NCT04476303)	BeyondBio	Aug 2020	Oct 2021
BMS-984923	Synaptic plasticity/neuroprotection	mGluR5 allosteric modulator	DMT	Recruiting; (NCT04805983)	Yale University, NIA	Mar 2021	Oct 2021
BDPP (bioactive dietary polyphenol preparation)	Proteostasis/ proteinopathies	Prevents Aβ and tau aggregation	DMT	Recruiting; (NCT02502253)	Johns Hopkins University, Mount Sinai School of Medicine	Jun 2015	Jun 2022
Contraloid acetate	Proteostasis/ proteinopathies	Aggregation inhibitor	DMT	Recruiting; (NCT04711486)	Charite University, Berlin, Germany	Dec 2020	Nov 2021
COR588	Synaptic plasticity/ neuroprotection	Lysine-gingipain inhibitor	DMT	Recruiting; (NCT04920903)	Cortexyme	Aug 2021	May 2022
Dabigatran	Vasculature	Direct thrombin inhibitor; reduce neurovascular damage	DMT	Not yet recruiting; (NCT03752294)	University of Rhode Island, ADDF, Boehringer Ingelheim	Nov 2018	Dec 2021
Donepezil	Neurotransmitter receptors	Cholinesterase inhibitor	Cognitive enhancer	Recruiting; (NCT04730635)	Merck	Mar 2021	Aug 2022
Edicotinib (JNJ-40346527)	Inflammation	CSF-1R antagonist; attenuates microglial proliferation and neurodegeneration	DMT	Not yet recruiting; (NCT04121208)	Janssen, University of Oxford	Nov 2020	Dec 2021
Efavirenz	Epigenetics	NNRTI; promote cholesterol removal; enhance amyloid reduction.	DMT	Active, not recruiting; (NCT03706885)	Case Western Reserve University, Cleveland Medical Center, Massachusetts General Hospital	May 2018	Dec 2022
Emtricitabine	Inflammation	NRTI; reduce neuroinflammation	DMT	Recruiting; (NCT04500847)	Butler Hospital, Alzheimer's Association, Brown University	Dec 2021	Aug 2023
IGC AD1	Neurotransmitter receptors	Tetrahydrocannabinol that binds to the CB1 receptor	Neuropsychiatric symptoms agent (agitation)	Recruiting; (NCT04749563)	IGC Pharma	Jan 2021	Jul 2021

(Continues)

TABLE 3 (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status (CT.gov ID)	Sponsor	Start date	Estimated end date
Lu AF87908	Tau	Monoclonal antibody to reduce tau	DMT	Recruiting; (NCT04149860)	Lundbeck	Sep 2019	Jul 2022
LX1001	Epigenetic	10hAPOE2, serotype rh. Ten AAV gene transfer vector expressing the cDNA coding for human *APOE* ε2, directly to the CNS/CSF of *APOE* ε4 homozygotes with AD	DMT	Recruiting; (NCT03634007)	Cornell University	Nov 2019	Jan 2024
LY3372993	Amyloid	Monoclonal antibody to reduce Aβ	DMT	Recruiting; (NCT04451408)	Eli Lilly	Jul 2020	Sep 2023
MK-1942 + donepezil	Neurotransmitter receptors	Undisclosed (MK-1942)	Cognitive enhancer	Recruiting; (NCT04308304)	Merck	Feb 2021	May 2022
NNI-362	Neurogenesis	Enhance neurogenesis; activates progenitor cells	DMT	Recruiting; (NCT04074837)	Neuronascent, NIA	Aug 2019	Dec 2020
REM0046127	Synaptic Plasticity/Neuroprotection	Regulates calcium dyshomeostasis; tau and Aβ reduction	DMT	Recruiting; (NCT04672135)	reMYND, NeuroScios GmbH	Nov 2020	May 2022
Salsalate	Inflammation	Non-steroidal anti-inflammatory to reduce inflammation	DMT	Active, not recruiting; (NCT03277573)	University of California, San Francisco	Jul 2017	Dec 2021
SHR-1707	Amyloid	Anti-amyloid monoclonal antibody	DMT	Recruiting; (NCT04973189) Recruiting; (NCT04745104)	Shanghai Hengrui Pharmaceutical Atridia Pty Ltd.	May 2021 Feb 2021	Nov 2021 May 2022
TB006	Tau	Anti-tau monoclonal antibody	DMT	Recruiting; (NCT04920786)	TrueBinding, Inc.	Jun 2021	Jan 2023
Telmisartan	Vasculature	Angiotensin II receptor blocker	DMT	Recruiting; (NCT02471833)	Emory University	Apr 2015	Feb 2022
Trehalose	Cell death	Induces autophagy and promotes clearance of aggregated proteins	DMT	Recruiting; (NCT04663854)	Mashhad University of Medical Sciences	Aug 2020	Aug 2022
Tricaprilin (AC-1202)	Metabolism and bioenergetics	Caprylic triglyceride	DMT	Recruiting; (NCT05028114)	Cerecin	Aug 2021	Dec 2022
Vorinostat	Epigenetics	Histone deacetylase (HDAC) inhibitor; enhanced synaptic plasticity	DMT	Recruiting; (NCT03056495)	German Center for Neurodegenerative Diseases, University Hospital, Bonn, University of Gottingen	Sep 2017	Mar 2022
VT301	Inflammation	Regulatory T cells	DMT	Recruiting; (NCT05016427)	VTBIO Co.	Nov 2020	Apr 2022
XPro1595	Inflammation	TNF inhibitor; reduce neuroinflammation	DMT	Recruiting; (NCT03943264)	Immune Bio, Alzheimer's Association	Nov 2019	Dec 2020

NOTE. Thirty agents in 31 Phase 1 clinical trial currently ongoing as of January 25, 2022 according to clinicaltrials.gov.

Abbreviations: Aβ, amyloid beta; AAV, adeno-associated virus; ADDF, Alzheimer's Drug Discovery Foundation; ApoE, apolipoprotein E; CADRO, Common Alzheimer's Disease and Related Disorders Research Ontology; CSF, cerebrospinal fluid; CSF-1R, colony-stimulating factor 1 receptor; DMT, disease-modifying therapy; GABA, gamma-aminobutyric acid; hTERT, human telomerase reverse transcriptase; NIA, National Institute on Aging; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; TNF, tumor necrosis factor.

TABLE 4 Stem cell therapy in clinical trials for Alzheimer's disease (ClinicalTrials.gov accessed January 25, 2022)

Agent	Phase	Status (CT.gov ID)	Sponsor	Subject characteristics	Amyloid evidence at entry
Allogeneic human MSCs	1	Active, not recruiting; (NCT04040348)	University of Miami	Mild to moderate AD with MMSE of 20 to 26	Amyloid PET or CSF
SNK01 (autologous natural killer cell)	1	Recruiting; (NCT04678453)	NKMax America	MCI or AD	Not required
Allogenic adipose MSC-Exosomes	1/2	Recruiting; (NCT04388982)	Ruijin Hospital, Cellular Biomedicine Group	Mild to moderate AD with MMSE of 10 to 24	Not required
CB-AC-02 (placenta derived MSCs)	1/2	Recruiting; (NCT02899091)	CHABiotech Co.	Mild to moderate AD with KMMSE of 10 to 26	Amyloid PET
Human umbilical cord blood-derived MSCs (NEUROSTEM)	1/2	Recruiting, extension study; (NCT03172117)	Medipost	Probable AD with KMMSE of 18 to 26	Amyloid PET
Allogeneic human MSCs	2	Recruiting; (NCT02833792)	Stemedica	Mild to moderate AD with MMSE of 12 to 24	Amyloid PET
AstroStem (autologous adipose-derived MSCs)	2	Not yet recruiting; (NCT04482413)	Nature Cell Co.	Mild AD with MMSE of 20 to 24	CSF amyloid

Abbreviations: AD, Alzheimer's disease; KMMSE, Korea Mini-Mental State Examination; MMSE, Mini-Mental State Examination; MSC, mesenchymal stem cell; PET, positron emission tomography.

3.5 | Biomarkers

Table 5 shows the biomarkers used as entry criteria or as outcome measures in current Phase 3 and Phase 2 AD clinical trials of DMTs as described on clinicaltrials.gov; these data may be incomplete as not all trial descriptions note if biomarkers are included in the trial.

Of the 31 Phase 3 DMT trials, six trials (19%) used amyloid positron emission tomography (PET) as an entry criterion and six (19%) used either amyloid PET or cerebrospinal fluid (CSF) amyloid measures. Five (16%) of the Phase 3 DMT trials used either CSF-amyloid/tau ratio or amyloid PET as an entry criterion, and one trial used plasma phosphorylated tau (p-tau) 217. Thirteen (42%) of Phase 3 DMT trials did not use biomarkers as study entry criteria. One Phase 3 trial of a cognitive enhancer used CSF amyloid or CSF tau for entry.

In Phase 2, 12 (14%) DMT trials used amyloid PET as an entry criterion, five (6%) used CSF amyloid or amyloid ratios, and 12 (14%) used either amyloid PET or CSF amyloid assessments. Six (7%) of the Phase 2 DMT trials used CSF-amyloid/tau ratio as an entry criterion, four (5%) used either CSF-amyloid/tau ratio or amyloid PET, three (4%) used tau PET, and one trial (1%) used either amyloid PET or CSF-tau. Thirty-nine (47%) of Phase 2 trials did not require biomarker-based diagnostic confirmation for study entry.

Of Phase 3 DMT trials, 19 (61%) used biomarkers as supportive outcomes. Ten (32%) used amyloid PET and seven (23%) used tau PET in support of clinical outcomes. In Phase 2, 46 DMT trials (55%) have biomarkers as supportive outcomes (11 amyloid PET; 10 tau PET).

TABLE 5 Biomarkers as outcome measures or as entry criteria in Phase 2 and Phase 3 DMT trials (clinicaltrials.gov accessed January 25, 2025)

	N of trials (%)	
Biomarker role in trial	Phase 3 DMTs	Phase 2 DMTs
Biomarker as an entry criterion[a]		
Amyloid PET	6 (19%)	12 (14%)
CSF amyloid	0	5 (6%)
Amyloid PET or CSF amyloid	6 (19%)	12 (14%)
CSF Aβ/tau ratio	0	6 (7%)
CSF Aβ/tau ratio or amyloid PET	5 (16%)	4 (5%)
Tau PET	0	3 (4%)
Amyloid PET or CSF tau	0	1 (1%)
Plasma tau	1 (3%)	0
Biomarker as an outcome measure[a]		
CSF amyloid	8 (26%)	20 (24%)
CSF tau	8 (26%)	24 (29%)
FDG-PET	2 (6%)	7 (8%)
vMRI	9 (29%)	15 (18%)
Plasma amyloid	4 (13%)	13 (16%)
Plasma tau	6 (19%)	9 (11%)
Amyloid PET	10 (32%)	11 (13%)
Tau PET	7 (23%)	10 (12%)

Abbreviations: CSF, cerebrospinal fluid; DMT, disease-modifying therapy; FDG, fluorodeoxyglucose; PET, positron emission tomography; vMRI, volumetric magnetic resonance imaging.
[a]Percentages refer to the percent of trials that used any biomarker as an outcome or the percent that used biomarkers as an entry criterion.

3.6 | Trial participants

Including all currently active trials, the total number of participants needed is 50,575. Of these, 37,184 are required for Phase 3

TABLE 6 Total person weeks contributed by participants for each type of trial (clinicaltrials.gov accessed January 25, 2022)

Phase	Type of trial	Average duration of treatment (weeks)	Total number of participants	Total participant weeks devoted to clinical trials
Phase 3	Prevention (preclinical AD)	159	7403	1,177,077
	DMT (not prevention)	87	23,050	2,005,350
	Cognitive enhancing	24	1960	47,040
	Psychotropic	18	5261	94,698
Phase 2	DMT	49	10,717	525,133
	Cognitive enhancing	27	735	19,845
	Psychotropic	8	486	3888
Phase 1	All	4	1453	5812
		Total		*3,878,843 weeks*

Abbreviations: AD, Alzheimer's disease; DMT, disease-modifying therapy.

TABLE 7 Trial sponsor for each phase of AD drug development and the number of trials of repurposed agents supported by each entity (clinicaltrials.gov accessed January 25, 2022)

	N of trials (%)				
Sponsor type	Phase 3	Phase 2	Phase 1	All phases	Repurposed agents
Biopharma Industry	32 (68%)	39 (41%)	15 (48%)	86 (50%)	13 (21%)
Academic medical centers/NIH	7 (15%)	34 (36%)	8 (26%)	49 (28%)	34 (56%)
Public-private partnerships (PPP)	5 (11%)	18 (19%)	6 (19%)	29 (17%)	7 (11%)
Others	3 (6%)	3 (3%)	2 (6%)	8 (5%)	7 (11%)

Abbreviations: AD, Alzheimer's disease; NIH, National Institutes of Health.

trials; 11,938 for Phase 2 trials; and 1453 for Phase 1 trials. Table 6 shows the major types of trials, the average duration in weeks of treatment exposure for each type of trial, and the number of participants required for each type of trial. This demonstrates that across all active trials, 3,878,843 participant-weeks will be devoted to clinical trials. This total is an underestimate as it does not include time devoted to screening prior to randomization or the time consumed in screen fails of individuals who do not progress to randomization. Nearly all trials (except Phase 1 trials) require a research partner that devotes an equal number of weeks to the trials making the total investment of time by participants and families ≈7,757,686 weeks or 148,777 years.

Recruitment of participants remains a major challenge and a key reason for the long duration of trials. Using the treatment period as a comparison, Phase 3 prevention and prodromal/mild AD dementia trials have approximately equal treatment and recruitment periods. Phase 3 mild-moderate AD dementia trials take 1.8 times longer to recruit participants than to assess treatment effects. In Phase 2, recruitment periods are consistently longer than exposure periods: 1.5 times longer for prevention trials, 2.2 times longer for prodromal/mild AD dementia trials, and 3.8 times longer for mild-moderate AD dementia.

3.7 | Trial sponsors

Across all trials, 50% are sponsored by the biopharma industry, 28% by academic medical centers (usually with funding from NIH), 17% are funded through public–private partnerships, and 5% are funded by other entities. In Phase 3, 68% of trials are sponsored by the biopharma industry, 15% by academic medical centers/NIH, 11% are public–private partnerships, and 6% are sponsored by others. In Phase 2, 41% of trials are sponsored by the biopharma industry, 36% by academic medical centers/NIH, 19% are public–private partnerships, and 3% are funded by others. Table 7 shows the sponsor of agents in each phase of development. Repurposed agents are more likely to have academic medical center/NIH sponsors (56%) and less likely to have industry sponsors (21%; Table 7).

3.8 | Global distribution of trials

Table 8 shows the global distribution of trials. We divided trials into those performed only in North America (United States and Canada); those conduced only outside of North America (excluding United States and Canada); and those conducted globally including North

TABLE 8 Global distribution of trials (clinicaltrials.gov accessed January 25, 2022)

	N of trials (%)		
	Phase 3	Phase 2	Phase 1
North America (United States & Canada) only	17 (36%)	51 (54%)	14 (45%)
Non-North America only	11 (23%)	30 (32%)	15 (48%)
North America and Non-North America	19 (40%)	13 (14%)	2 (6%)

American and non-North American sites combined. Thirty-six percent of Phase 3 trials involved only North America and 40% included North American and non-North American countries (76% of trials include North American sites with or without sites in other global regions). Phase 2 trials are more often conducted only in North America (54%); North America is included as a trial location in 64% of trials (trials done in North America only plus those conducted in North American and non-North American sites together). Some Phase 1 trials conducted outside the United States may not be registered on clinicaltrials.gov and may have gone undetected in this review. Across all phases, 48% of trials are conducted only in North America; 33% are conducted only outside of North America; and 20% are conducted with both North American and non-North American sites participating. North America participates in 67% of all trials registered on clinicaltrials.gov.

4 | DISCUSSION

Development of new therapies for diseases of the nervous system is challenging with high failure rates and long development times forcing some major pharmaceutical companies to stop investing in this area of drug development.[18] Of the 49 novel drugs approved by the FDA in 2021, seven were for treatment of disorders of the central nervous system (CNS) and two were for the peripheral nervous system disorders (Duchenne muscular dystrophy, myasthenia gravis; fda.gov).[19] The CNS disorders with new treatments were migraine, von Hippel-Lindau disease (including CNS hemangioblastomas), schizophrenia, relapsing multiple sclerosis, attention deficit-hyperactivity disorders (two drugs approved), and AD. The AD drug approval is the first in the United States since 2003.

The AD drug development pipeline comprises 143 agents in 172 trials (Figure 1). There are 31 agents in Phase 3, 82 in Phase 2, and 31 in Phase 1. DMTs are the agents most included in the pipeline. One hundred nineteen putative DMTs are being assessed (21 in Phase 3, 71 in Phase 2, 27 in Phase 1). DMTs represent 83.2% of the pipeline of agents. There are 14 cognitive enhancers and 10 drugs targeting neuropsychiatric symptoms in the pipeline. The 143 agents in the pipeline compares to 126 in the pipeline in 2021;[10,11] this apparent increase may be partially attributable to our improved search techniques.

Aducanumab is the first DMT approved by the US FDA for the treatment of AD. It is the second DMT approved in the United States for any neurodegenerative disease, the other is edaravone used in the treatment of amyotrophic lateral sclerosis.[20] The approval of aducanumab used an accelerated regulatory mechanism based on demonstration of amyloid plaque lowering considered reasonably likely to predict clinical benefit.[21] The accelerated pathway may be used for other anti-amyloid plaque-lowering antibodies currently under review by the FDA (donanemab and lecanemab).[3–5] The trials of gantenerumab will be completed in 2022 and may lead to a request for marketing approval based on conventional clinical outcomes.[22,23] Other biomarkers may eventually be qualified as surrogate outcomes predictive of clinical benefit. Surrogate outcomes facilitate drug development.[24]

MCI due to AD and mild AD dementia comprise the most common population included in current clinical trials accounting for 36% of Phase 3 trials and 52% of Phase 2 trials.[25] These trials may be most impacted by the approval of aducanumab for this same population. Trial patients eligible for aducanumab may wish to begin active therapy rather than remain in a placebo-controlled trial that will last many months; patients appropriate for treatment with aducanumab and eligible for trial participation may prefer active treatment to trial enrollment; or patients on aducanumab may wish to continue this treatment and be included in trials of potential new AD therapies in addition to their ongoing treatment. Trial design will require reconsideration to account for the presence of aducanumab in the market.[26] Among the trial design options are to exclude patients on aducanumab from participation in a trial assessing a new therapy as is currently done in some AD trials that exclude cholinesterase inhibitors or memantine. Another option is to allow aducanumab as background therapy with stratification, analytic adjustment, and recalculation of sample sizes required to show a treatment effect. Trials comparing a novel agent to aducanumab may be conducted with superiority or a non-inferiority design with clinical efficacy, biomarker effects, or safety as primary or key secondary outcomes. AD therapeutic research can build on lessons learned from multiple sclerosis where multiple DMTs have been approved using a variety of assessment strategies.[27]

The CADRO classification of targets reveals a proliferation of mechanistic treatment approaches to AD including agents directed at amyloid (20 agents), tau (13 agents), inflammation (23 agents), and synaptic plasticity (19 agents). Altogether 15 of the 17 categories (excluding "unknown" and "other") are represented by drugs in the pipeline (Figure 4).

Seven monoclonal antibodies, one active vaccine, one ASO, and four small molecules directed at aspects of the biology of the tau protein and neurofibrillary tangle formation are currently in AD clinical trials. The antibodies are directed primarily at extracellular tau that is transferred from cell to cell in a prion-like manner. Several tau monoclonal antibodies have failed to establish a drug–placebo difference in recent AD trials including semorinemab, zagotenemab, gosuranemab, and ABBV-8E12.[28,29]

Targets for monoclonal antibodies in the current AD pipeline other than the canonical amyloid and tau proteins include antibodies directed at TREM2, CD38, semaphorin 4D, and galactin 3.

The SARS-CoV-2 virus and ensuing pandemic have challenged trial sites and temporarily slowed drug development. Many COVID-related

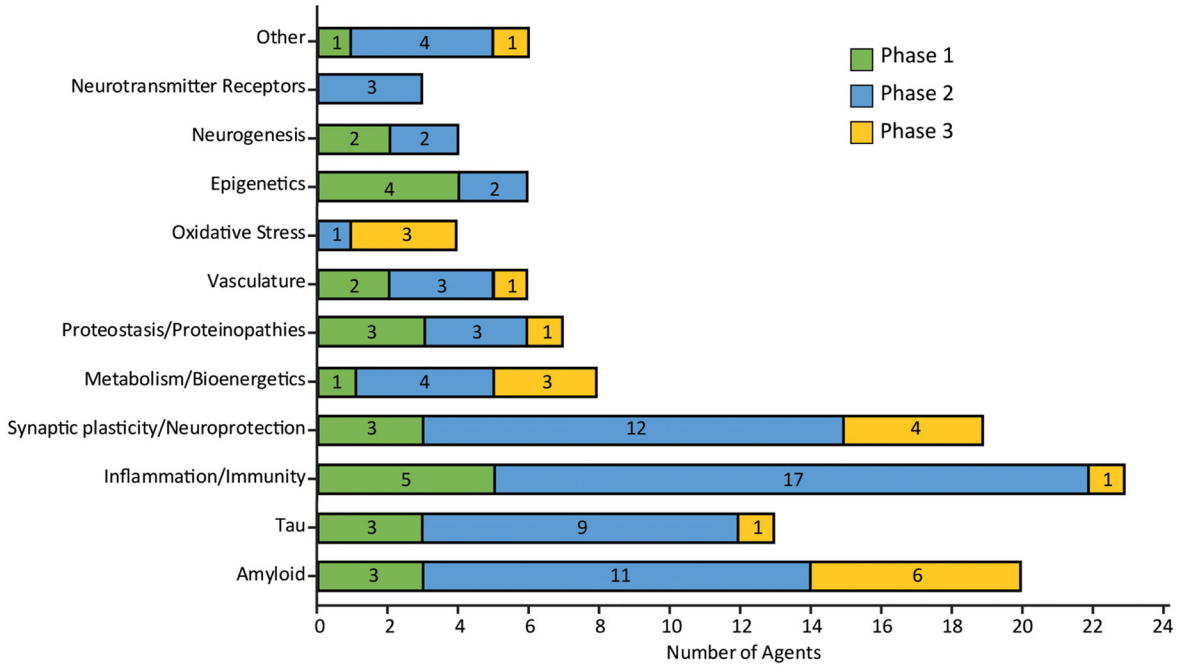

FIGURE 4 Mechanisms of action of disease modifying agents in all phases of clinical trials grouped according to the Common Alzheimer's Disease Research Ontology (CADRO) (Figure © J Cummings; M de la Flor, PhD, Illustrator)

issues affected trial sites including temporary or permanent site closure; delayed recruitment; participant reluctance to visit sites for clinical assessments and laboratory tests; patient and care partner decisions to stop trial participation; difficulty providing drugs to participants not visiting sites; the change of on-site testing stemming from masks, shields, and COVID testing procedures; the need to develop unanticipated strategies for remote data collection and laboratory testing; the requirement to adjust procedures to obtain or renew informed consent remotely; illness and death of trial participants; and illness, death, and resignation of trial site staff.[30] The FDA provided guidance of Good Clinical Practice of trial conduct during the pandemic.[31,32] The FDA also provided guidance on statistical and analytic considerations for data from trials affected by the COVID pandemic.[31] Many AD trial outcomes were successfully administered using telemedicine without compromise of data reliability.[33] Statistical modeling and trial simulation of AD trials indicated that stopping trials usually resulted in substantial loss of power and prolonging or enlarging trials were strategies to preserve trial integrity.[34] Despite the many challenges posed by the SARS-CoV-2 pandemic, the AD trial ecosystem proved to be resilient with few trials stopped during the pandemic and a substantial number of new trials initiated.

The increased use of composite outcomes is apparent in this review. This trend is especially evident in trials in early AD (MCI due to AD and mild AD dementia) in which a significant drug–placebo difference on a single primary outcome measure may be the basis for regulatory approval. Many trials in this stage of the disease use the Clinical Dementia Rating–Sum of Boxes (CDR-SB) as the primary outcome.[35] Phase 2 trials have used a greater diversity of primary clinical outcomes. The Phase 2 trial of lecanemab used the Alzheimer's Disease Composite Score (ADCOMS)—an analytic approach using the all items of the CDR and elements of the MMSE and Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog)—as an outcome and as a guide to dose decisions in the Bayesian dose-finding portion of the study.[5,36] The Phase 2 trial of donanemab used the integrated Alzheimer's Disease Rating Scale (iADRS) comprising the ADAS-Cog-13 and the Alzheimer's Disease Cooperative Study (ADCS) instrumental Activities of Daily Living (iADL) scale as the primary clinical outcome measure. Composite endpoints, when appropriately constructed and interpreted, provide greater measurement efficiency and can facilitate efficacy conclusions with smaller sample sizes.[37]

Biomarkers play increasingly informative roles in AD trials. The Phase 2 trial of donenemab used tau PET to define the population, requiring the presence of tau but without a high level of tau abundance suggesting advanced disease.[4] Nearly all the participants meeting the tau PET criteria had positive amyloid imaging; the discordance was 0.9% of individuals who met the tau PET criteria and not the amyloid PET criteria. This supports the observation that the presence of moderate levels of tau are highly predictive of the amyloid plaque burden.[38,39] Plasma p-tau is highly correlated with amyloid PET[40,41] and is being used to identify participants for some AD trials (e.g., Trailblazer 3). If confirmed, use of p-tau to identify individuals for AD trials is anticipated to simplify and accelerate AD trial recruitment.

Other notable observations from this pipeline review include the large number of participants needed for all ongoing trials (50,757) and the tremendous amount of participant time devoted to trials (3,878,843 weeks spent in trials). The long periods required for participant recruitment are documented in this review; many trials have recruitment periods that exceed the treatment period by 2-fold. The key role played by the biopharmaceutical industry in drug development is highlighted by the observation that industry sponsors 68% of

all Phase 3 trials and 41 percent of all Phase 2 trials. The NIH and academic medical centers play a large role in Phase 2 proof-of-concept studies (36% of trials) and a smaller role in late-stage drug development (15% of Phase 3 trials). Repurposed agents have a greater role in proof-of-concept and are more likely to be funded by NIH (56%) than biopharmaceutical sponsors (21%).[42] Global participation in drug development is evident in this review. Sixty-three percent of Phase 3 trials and 46% of Phase 2 trials include non-North American sites.

This review is based on data from the clinical trials registry, clinicaltrials.gov. Recent studies support the use of this data source. Venugopal and Saberwal showed that clinicaltrials.gov is more comprehensive than any other of the 18 worldwide registries they reviewed.[15] The FDA Amendments Act of 2007 requires reporting of trial results within 1 year of trial completion and the FDA and NIH are increasingly vigilant about enforcement of this mandate, further strengthening the data available from the registry.[43] The registry and our search strategies are imperfect, and some agents may have been omitted in this review.

5 | SUMMARY

Clinical trials for AD target a robust array of biological processes including most of those identified in the CADRO classification. Amyloid therapies have shown progress with approval of the monoclonal antibody aducanumab. Other amyloid approaches as well as treatments for tau abnormalities, inflammation, and synaptic dysfunction are well represented in the AD drug development pipeline. The number of clinical trials has increased somewhat despite challenges created by the current pandemic. Biomarkers are increasingly used to inform clinical trials including their use in diagnosis and as outcomes. New clinical outcome measures, especially composite scale and scores, provide greater sensitivity to treatment response. Drug development for AD depends on robust alliances with participants and their families given the large time sacrifices they make in trial involvement. The distribution of sites in trials demonstrates the global ecosystem that supports AD drug development. Progress in target identification, drug discovery, and clinical trial methodology increases confidence that more and better treatments will emerge from the AD drug development pipeline.

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CONFLICTS OF INTEREST

Jeffrey Cummings has provided consultation to Acadia, Alkahest, AlphaCognition, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Biohaven, Cassava, Cerecin, Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, Grifols, Janssen, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Ono, Otsuka, PRODEO, ReMYND, Renew, Resverlogix, Roche, Signant Health, Suven, United Neuroscience, and Unlearn AI pharmaceutical, assessment, and investment companies. Jeffrey Cummings owns the copyright of the Neuropsychiatric Inventory. Garam Lee is a full-time employee of Biogen. Kate Zhong provides consultation to Green Valley Pharmaceuticals. Pouyan Nahed has no disclosures. Mina Esmail Zadeh Nojoo Kambar has no disclosures. Jorge Fonseca has no disclosures. Kate Zhong has no disclosures.

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