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REVIEW ARTICLE

Alzheimer's disease drug development pipeline: 2023

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Abstract

Introduction: Drugs that prevent the onset, slow progression, or improve cognitive and behavioral symptoms of Alzheimer's disease (AD) are needed.

Methods: We searched ClinicalTrials.gov for all current Phase 1, 2 and 3 clinical trials for AD and mild cognitive impairment (MCI) attributed to AD. We created an automated computational database platform to search, archive, organize, and analyze the derived data. The Common Alzheimer's Disease Research Ontology (CADRO) was used to identify treatment targets and drug mechanisms.

Results: On the index date of January 1, 2023, there were 187 trials assessing 141 unique treatments for AD. Phase 3 included 36 agents in 55 trials; 87 agents were in 99 Phase 2 trials; and Phase 1 had 31 agents in 33 trials. Disease-modifying therapies were the most common drugs comprising 79% of drugs in trials. Twenty-eight percent of candidate therapies are repurposed agents. Populating all current Phase 1, 2, and 3 trials will require 57,465 participants.

Discussion: The AD drug development pipeline is advancing agents directed at a variety of target processes.

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

HIGHLIGHTS

- There are currently 187 trials assessing 141 drugs for the treatment of Alzheimer's disease (AD).
- Drugs in the AD pipeline address a variety of pathological processes.
- More than 57,000 participants will be required to populate all currently registered trials.

1 | INTRODUCTION

Alzheimer's disease (AD) is increasing at an alarming pace as the population of the United States and the world age. There are an estimated 6.2 million individuals with AD dementia in the United States and an estimated 50 million individuals with AD dementia globally. These populations will grow to 12.7 million and 150 million in the United States and globally, respectively, by 2050.[1,2] In addition to AD dementia, there are an approximately equal number of individuals with prodromal AD and an even larger number of persons with preclinical AD characterized by normal cognition, biomarkers consistent with AD pathology, and an increased risk for progression to cognitive impairment.[2,3] These epidemiologic predictions make it increasingly urgent that new medications to prevent the onset, delay progression, or improve symptoms of AD be found.

The goal of this review is to describe the current AD drug development pipeline; note trends in clinical trial design, clinical outcome measures, and biomarker use in trials; and review which drug mechanisms of action (MoAs) and biological targets are being pursued. Monoclonal antibodies and other biological agents in the current AD pipeline are discussed, small molecules intended to produce disease modification currently in clinical trials are reviewed, and symptomatic agents seeking to produce cognitive enhancement or reduce neuropsychiatric symptoms in AD are reported. This review is based on data derived from the ClinicalTrials.gov registry. The report follows the approach of our previous annual reviews of the AD drug development pipeline.[4,5]

RESEARCH IN CONTEXT

1. **Systemic Review**: Alzheimer's disease (AD) represents a complex disorder for which there are few treatments. Candidate therapies for AD are assessed in clinical trials and are registered on ClinicalTrials.gov. We reviewed clinical trials and the drugs being assessed to understand the flow of drugs from laboratories to the clinic.
2. **Interpretation**: There are currently 187 Phase 1, 2, and 3 clinical trials assessing 141 unique drugs. Thirty-six drugs are being assessed in Phase 3, 87 in Phase 2, and 31 in Phase 1. Transmitter receptors, amyloid, synaptic function, and inflammation are the most common targets of drugs in the pipeline.
3. **Future Directions**: Clinical trials represent the only means of generating efficacy and safety data that can lead to drug approval and widespread availability. The AD drug development pipeline includes agents addressing a variety of targets and intended for different phases of AD. Incentives for AD drug development are needed.

2 | METHODS

The US National Library of Medicine of the National Institutes of Health (NIH) maintains a clinical research registry, ClinicalTrials.gov, which serves as the source of information for this review. The US Food and Drug Administration (FDA) Amendments Act requires that all clinical trials be registered on ClinicalTrials.gov. The "Common Rule" governing ClinicalTrials.gov requires registration for studies that meet the definition of an "applicable clinical trial" (HR3580, 2007). Registration must occur within 21 days of enrolling the first patient in the trial. Studies of compliance with the Common Rule indicate that compliance with the rule is high and most trials are registered appropriately.[6,7] The United States has more clinical trials than any other country, ClinicalTrials.gov includes most therapies currently in clinical trials for AD globally, and ClinicalTrials.gov is more comprehensive than any other trial registry.[8] The information in this review can be regarded as comprehensive but not exhaustive.

The index date for this review is January 1, 2023, and the text and tables apply to the information as registered on ClinicalTrials.gov on this date. We searched all terms related to AD and mild cognitive impairment (MCI) for inclusion in the review. We do not include studies whose participants have dementia of any cause or in which AD is included with other dementias not separated by inclusion and exclusion criteria. We do not include trials in which the MCI is specified to be part of a non-AD disease such as MCI of Parkinson's disease. We include all trials of agents in Phases 1, 2, and 3. We did not include Phase 4 trials or trials without a phase designation. If a trial is designated as 1/2 or 2/3 we include it with trials of the higher number. We archive information on the trial agent, trial title, trial number assigned on ClinicalTrials.gov, start date, projected primary end date, duration of treatment exposure, number of arms of the study (usually a placebo arm and one or more treatment arms with different doses), whether a biomarker was collected at entry or as an outcome, whether the agent was repurposed, and where the trials were performed. We use the "funder type" trial sponsorship categories specified on ClinicalTrials.gov (the biopharmaceutical industry; public– private partnership; NIH and related including individuals, universities, and organizations; and "other" [non-NIH] federal entities). We identified "public–private partnerships" as any trial in which a biopharmaceutical company was one of two or more sponsors for the trial. We included trials labeled as recruiting, active but not recruiting (i.e., trials that have completed recruitment and are continuing with the exposure portion of the trial), enrolling by invitation (i.e., open-label extensions of trials limited to those participating in the double-blind portion of the trials), and not yet recruiting (i.e., registered on ClinicalTrials.gov but no patients have been enrolled). We note if the trial population comprises participants with preclinical AD (cognitively normal with biomarker evidence of AD or an autosomal dominant AD-causing mutation participating in AD prevention trials), MCI, AD dementia (mild, moderate, severe), or healthy volunteers. We note the trials listed as completed, terminated, suspended, unknown, or withdrawn since the last index date. The report does not include trials of non-pharmacologic therapeutic approaches such as exercise trials, cognitive-behavior therapies, caregiver interventions,

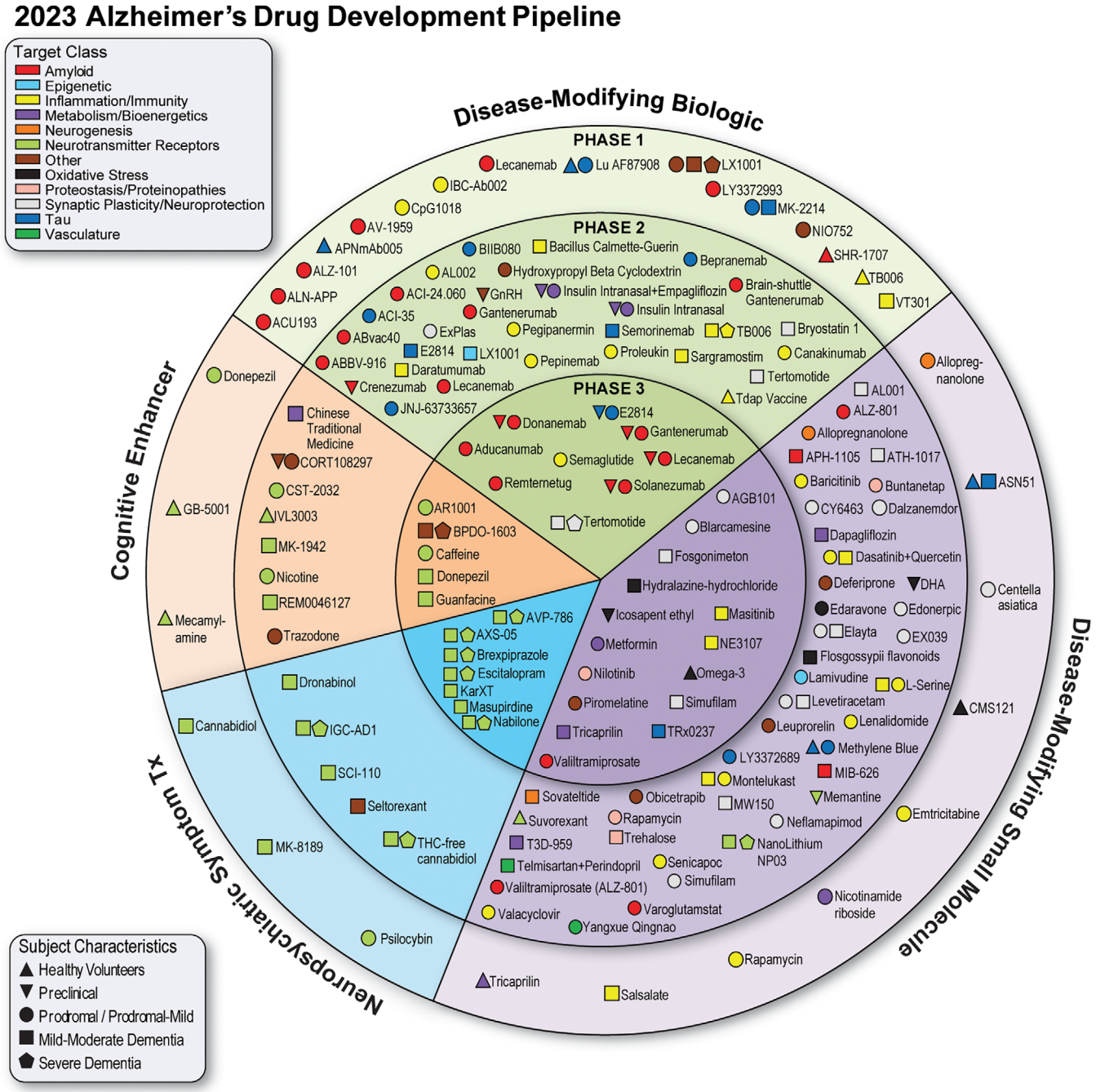

FIGURE 1 Agents in clinical trials for treatment of Alzheimer's disease in 2023 (from ClinicalTrials.gov as of the index date of January 1, 2023). The inner ring shows Phase 3 agents; the middle ring comprises Phase 2 agents; the outer ring presents Phase 1 therapies; agents in green areas are biologics; 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 CADRO-based class of the agent ("Other" category includes CADRO classes that have three or fewer agents in trials). CADRO, Common Alzheimer's Disease Research Ontology; Tx, treatment. (Figure © J Cummings; M de la Flor, PhD, Illustrator).

supplements, medical foods, or devices. We do not include trials of biomarkers if no intervention is being tested; we note whether biomarkers were collected at trial entry or were included as outcome measures in the intervention trials we report. Cell therapies are included among the interventions described (they are not included in Figure 1).

We use the Actual Study Start Date as listed on ClinicalTrials.gov for the beginning of the trial and the Estimated Primary Completion Date for the anticipated end of the trial. The total trial duration is the projected period between the actual study start date and the estimated primary completion date. The treatment exposure duration is specified on ClinicalTrials.gov; the recruitment period

is calculated as the total trial duration minus the treatment study period.

The Common Alzheimer's Disease Research Ontology (CADRO) of the National Institute on Aging and the Alzheimer's Association; the International Alzheimer's and Related Dementias Research Portfolio (IADRP; iadrp.nia.nih.gov) provides the basis for the description of the biological processes in AD that comprise possible targets for therapeutic intervention. The CADRO Translational Research and Clinical Interventions Category lists potential targets for AD clinical therapies. The targets include amyloid beta; 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. These processes/targets are used to classify the target category of the agents. Some agents may have more than one MoA; for these, we reviewed the literature to identify the putative predominant mechanisms.

Treatments whose purpose is cognitive enhancement or control of neuropsychiatric symptoms without claiming to impact the underlying biological causes of AD are classified as "symptomatic." Treatments intended to change the biology of AD and slow the course of the disease are listed as "disease modifying." If the sponsor did not specify the therapeutic purpose, we used the features of the trial (e.g., clinical outcomes, trial duration, use of biomarkers for participant inclusion, use of biomarkers as outcomes, number of participants) to infer if a trial was structured to demonstrate disease modification or symptomatic benefit. We divided disease-modifying therapies (DMTs) into biologics (e.g., monoclonal antibodies, vaccines, antisense oligonucleotides [ASOs], gene therapy, etc.) and small molecules (e.g., drugs typically taken orally and less than 500 Daltons in molecular weight).

To determine whether an agent is approved for a non-AD indication and considered a repurposed agent in the pipeline, we used the currently available version of DrugBank (https://go.drugbank.com/).

We downloaded all the original data using the ClinicalTrials.gov application programming interface (API) (https://clinicaltrials.gov/api/gui). We implemented an automated Python script-based computational database platform to search for the appropriate trials on ClinicalTrials.gov and to interrogate and analyze data from the derived database. As an initial filtering step, we identified all the interventional trials designed with the primary purpose of prevention, treatment, or basic science, and including at least one intervention type including drug, dietary supplement, or biological. We then eliminated all non-drug trials. Stem cell trials were assembled separately. If questions arose during the analytic process about the nature of the intervention or other trial aspects, they were resolved by expert curation. We generated summary statistics (e.g., mean and count) using the annotated trial data for all analyses.

3 | RESULTS

3.1 | Overview

There were 187 Phase 1, 2, or 3 clinical trials assessing 141 unique treatments for AD as of the index date of January 1, 2023. There were 36 agents in 55 Phase 3 trials, 87 agents in 99 Phase 2 trials, and 31 agents in 33 Phase 1 trials (some agents are in more than one trial; Figure 1). Among the Phase 1, 2, and 3 trials, the most common agents being studied are DMTs (111 agents; 78% of the total number of drugs in these trials). Symptomatic agents comprise 21% (N = 30) of the pipeline including 15 (11% of all agents in Phase 1, 2, or 3 trials) cognitive enhancers and 15 (11% of all agents in these trials) psychotropic agents. Of the DMTs, there were 49 (44% of DMTs) biologics and 62 (56% of DMTs) small molecules. From the target perspective, 22 (16%) of agents have amyloid, 13 (9%) tau, 24 (17%) inflammation, 18 (13%) synaptic plasticity/neuroprotection, 10 (7%) metabolism and bioenergetics, 7 (5%) oxidative stress, and 4 (3%) proteostasis/proteinopathy as their primary mechanistic targets. Twenty-eight agents (29%) have neurotransmitters as their biological target; this class includes cognitive-enhancing agents and drugs being developed to reduce neuropsychiatric symptoms. Sixteen drugs (11%) target processes represented by only one to three agents per CADRO category. Considering DMTs only, 24 (67%) of Phase 3 agents are DMTs; 74 (85%) Phase 2 drugs are DMTs; and 25 (81%) of Phase 1 agents are DMTs. There are 40 repurposed agents in the pipeline comprising 28% of candidate therapies (all phases combined). There are eight ongoing trials involving stem cell therapies. Since January 25, 2022, 31 trials have been completed, 2 were suspended, 15 are of unknown status, and 1 each was terminated or withdrawn. Fifty-eight new trials (16 in Phase 1, 27 in Phase 2, 15 in Phase 3) have entered the pipeline in the past year (since index date of January 25, 2022).

3.2 | Phase 3

Phase 3 has 36 agents in 55 trials (Figure 1, Figure 2, and Table 1). DMTs represent 67% (N = 24) of agents in Phase 3 trials including 9 (25% of the Phase 3 agents) biologics and 15 (42%) small molecules. Five (14% of Phase 3 agents) are putative cognitive-enhancing agents and seven (19%) drugs target neuropsychiatric symptoms of AD. CADRO mechanisms represented among Phase 3 agents include amyloid (7 agents; 19%), synaptic plasticity/neuroprotection (6; 17%), oxidative stress (3; 8%), metabolism and bioenergetics (3; 8%), tau (2; 6%), inflammation (2; 6%), proteostasis/proteinopathies (1; 3%), and circadian rhythm (1; 3%). Eleven agents in Phase 3 (31%) address transmitter receptor mechanisms. Figures 1 and 2 show the CADRO-based MOAs of agents in Phase 3. Twelve (33%) of Phase 3 agents are repurposed treatments approved for use in another indication (6 = DMT; 3 = for cognitive enhancement; 3 = for treatment for behavioral symptoms). Six trials

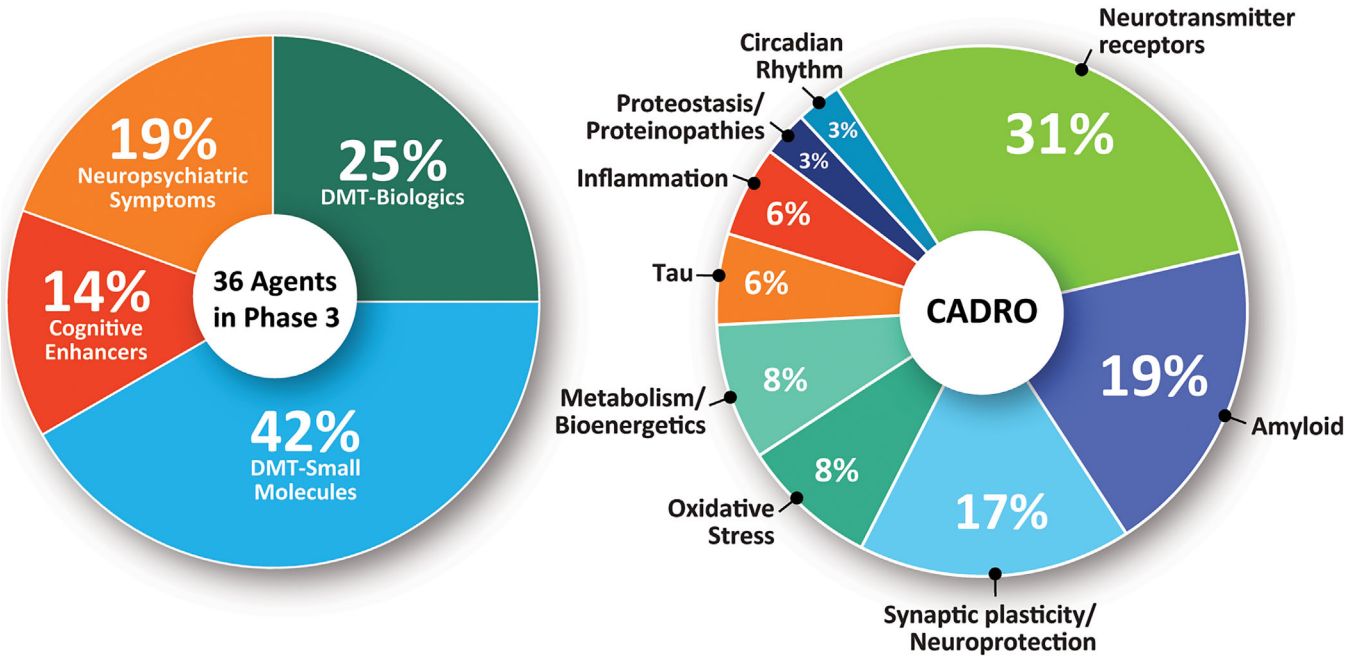

FIGURE 2 Mechanisms of action of agents in Phase 3 (as classified using the CADRO approach). CADRO, Common Alzheimer's Disease Research Ontology; DMT, disease-modifying therapy. (Figure © J Cummings; M de la Flor, PhD, Illustrator).

that were active in 2022 were completed, one was suspended, and one is of unknown status. Fifteen Phase 3 trials were initiated between January 25, 2022, and January 1, 2023.

Five of the trials in Phase 3 are prevention trials enrolling cognitively normal participants, 25 trials enroll early AD defined as MCI/prodromal AD and mild AD dementia (45% of all Phase 3 trials), 11 trials include participants with mild-to-moderate AD or moderate AD dementia, 8 enroll moderate-to-severe or severe participants, and 6 trials enroll participants with AD dementia of any severity.

Taken together currently active trials in Phase 3 require a total enrollment of 41,864 participants. Prevention trials require 5565 participants with preclinical AD; trials of MCI due to AD or prodromal AD require 2284 participants; trials focusing on early AD (prodromal AD or mild AD dementia) require 20,482 participants; trials for mild-to-moderate or moderate AD dementia plan to enroll 6359 participants; and trials of moderate-to-severe and severe AD plan enrollment of 4546 participants. Phase 3 DMT trials of biologics require 24,528 participants; DMT small molecule trials will enroll 9450; cognitive enhancer trials plan enrollment of 2360 participants; and trials of drugs being developed for neuropsychiatric syndromes plan enrollment of 5526 participants.

DMT trials assessing biological agents enroll a mean of 1168 participants, DMT trials testing small molecules enroll a mean of 556 individuals, cognitive enhancer trials enroll of a mean of 393 persons per trial, and trials of neuropsychiatric syndrome therapies enroll a mean of 502 participants.

Mean treatment exposure period for prevention trials of DMT biologics was 143 weeks and for DMT small molecules was 78 weeks. DMT trials for symptomatic patients averaged 103 weeks for biologics and 56 weeks for small molecule trials. Cognitive enhancer trials had an average of 25 treatment weeks. Trials for the treatment of neuropsychiatric syndromes had a mean of 19 treatment weeks.

Recruitment is a major challenge for clinical trials. The average recruitment (calculated as the total trial duration minus the treatment period) time for prevention trials of DMT biological agents was 107 and for DMT small molecules was 233 weeks. Non-prevention DMT trials required 147 weeks for biologics and 99 weeks for small molecules. Cognitive enhancer trials had mean recruitment times of 142 weeks. Recruitment time for trials of treatments for neuropsychiatric syndromes had a mean of 194 weeks.

3.3 | Phase 2

Phase 2 has 87 agents in 99 trials (Figure 1, Figure 3, and Table 2). DMTs represent 85% ($N = 74$) of agents in Phase 2 trials including 31 (36% of the Phase 2 agents) biologics and 43 (49%) small molecules. Eight (9% of Phase 2 agents) are putative cognitive enhancing agents and five (6%) drugs target neuropsychiatric symptoms of AD. CADRO mechanisms represented among Phase 2 treatments include inflammation (17 agents; 20%), synaptic plasticity/neuroprotection (14; 16%), transmitter receptors (12; 14%), amyloid (11 agents; 13%), tau (8; 9%), metabolism and bioenergetics (5; 6%), oxidative stress (3; 3%), proteostasis/proteinopathies (3; 3%), growth factors and hormones (3; 3%), *APOE* and lipids (3; 3%), vasculature (2; 2%), circadian rhythm (2; 2%), neurogenesis (2; 2%), epigenetic regulators (1; 1%), and cell death (1; 1%). Figures 1 and 3 show the CADRO-based targets of agents in Phase 2. Twenty-four (28%) of the Phase 2 agents are repurposed

TABLE 1 Agents in Phase 3 of Alzheimer's disease drug development (ClinicalTrials.gov accessed January 1, 2023).

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
Aducanumab	DMT, biologic	Amyloid beta	Anti-amyloid monoclonal antibody directed at plaques and oligomers	NCT04241068	Biogen	Mar 2020	Oct 2023
				NCT05310071	Biogen	Jun 2022	Dec 2025
AGB101	DMT, small molecule	Synaptic plasticity/ neuroprotection	SV2A modulator; CA3 area downregulation	NCT03486938	AgeneBio	Jan 2019	Dec 2022
AR1001	Sx, cognition	Neurotransmitter receptors	Phosphodiesterase 5 inhibitor increases intracellular cGMP promoting synaptic plasticity	NCT05531526	AriBio Co., Ltd.	Dec 2022	Dec 2025
AVP-786	Sx, behavior	Neurotransmitter receptors	NMDA receptor antagonist, sigma 1 receptor agonist; serotonin and norepinephrine transporter inhibitor	NCT02446132	Otsuka Pharmaceutical Development & Commercialization, Inc.	Dec 2015	Oct 2023
				NCT03393520	Otsuka Pharmaceutical Development & Commercialization, Inc.	Oct 2017	Jul 2023
				NCT04408755	Otsuka Pharmaceutical Development & Commercialization, Inc.	Jul 2020	Dec 2024
				NCT04464564	Otsuka Pharmaceutical Development & Commercialization, Inc.	Sep 2020	Dec 2024
AXS-05	Sx, behavior	Neurotransmitter receptors	NMDA receptor antagonist, sigma 1 receptor agonist; serotonin and norepinephrine transporter inhibitor	NCT04947553	Axsome Therapeutics, Inc.	Jun 2021	Jun 2023
				NCT05557409	Axsome Therapeutics, Inc.	Sep 2022	Jun 2025
Blarcamesine (Anavex 2-73)	DMT, small molecule	Synaptic plasticity/ neuroprotection	Sigma-1 receptor agonist, M2 autoreceptor antagonist	NCT04314934	Anavex Life Sciences Corp.	Oct 2019	Jul 2024
BPDO-1603	Sx, cognition	Synaptic plasticity/ neuroprotection	Undisclosed	NCT04229927	Hyundai Pharmaceutical Co., LTD.	Feb 2020	Feb 2022
Brexpiprazole	Sx, behavior	Neurotransmitter receptors	Atypical antipsychotic; D2 receptor partial agonist and serotonin-dopamine modulator	NCT03620981	Otsuka Pharmaceutical Co., Ltd.	Aug 2018	Mar 2023
Caffeine	Sx, cognition	Neurotransmitter receptors	Adenosine antagonist; non-specific phosphodiesterase inhibitor	NCT04570085	University Hospital, Lille	Mar 2021	Nov 2024
Donanemab	DMT, biologic	Aβ	Anti-amyloid monoclonal antibody specific for pyroglutamate plaque amyloid	NCT04437511	Eli Lilly and Company	Jun 2020	Apr 2023
				NCT05026866	Eli Lilly and Company	Aug 2021	Oct 2027
				NCT05108922	Eli Lilly and Company	Nov 2021	Sep 2022
				NCT05508789	Eli Lilly and Company	Oct 2022	Apr 2027

(Continues)

TABLE 1 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
Donepezil	Sx, cognition	Neurotransmitter receptors	Acetylcholinesterase inhibitor; adipokine modulation	NCT04661280	Assistance Publique—Hôpitaux de Paris	Feb 2022	Aug 2024
				NCT05592678	The University of Texas Health Science Center at San Antonio	Feb 2023	Feb 2027
E2814	DMT, biologic	Tau	Anti-tau monoclonal antibody	NCT01760005	Washington University School of Medicine	Dec 2012	Oct 2027
				NCT05269394	Washington University School of Medicine	Dec 2021	Jul 2027
Escitalopram	Sx, behavior	Neurotransmitter receptors	Selective serotonin reuptake inhibitor	NCT03108846	JHSPH Center for Clinical Trials	Jan 2018	Dec 2021
Fosgonimeton (ATH-1017)	DMT, small molecule	Synaptic plasticity/ neuroprotection	Hepatocyte growth factor (HGF); activates signaling via the HGF/MET receptor system; promotes survival of neurons, enhances hippocampal synaptic plasticity	NCT04488419	Athira Pharma	Sep 2020	Sep 2022
Gantenerumab	DMT, biologic	Aβ	Anti-amyloid monoclonal antibody directed at amyloid oligomers and plaque	NCT01760005	Washington University School of Medicine	Dec 2012	Oct 2027
				NCT03443973	Hoffmann-La Roche	Aug 2018	Sep 2022
				NCT03444870	Hoffmann-La Roche	Jun 2018	Dec 2022
				NCT04339413	Hoffmann-La Roche	May 2020	Jan 2023
				NCT04374253	Hoffmann-La Roche	Feb 2021	Feb 2023
				NCT05256134	Hoffmann-La Roche	Apr 2022	Mar 2023
				NCT05552157	Washington University School of Medicine	Dec 2022	Nov 2029
Guanfacine	Sx, cognition	Neurotransmitter receptors	Alpha-2 adrenergic agonist	NCT03116126	Imperial College London	Jan 2019	Dec 2022
Hydralazine hydrochloride	DMT, small molecule	Oxidative stress	Free radical scavenger	NCT04842552	Shahid Sadoughi University of Medical Sciences and Health Services	Aug 2021	Jun 2023
Icosapent ethyl	DMT, small molecule	Oxidative stress	Purified form of the omega-3 fatty acid eicosapentaenoic acid (EPA)	NCT02719327	VA Office of Research and Development	Jun 2017	Sep 2023
KarXT (Xanomeline + Trospium)	Sx, behavior	Neurotransmitter receptors	Muscarinic cholinergic agonist with peripheral anticholinergic agent	NCT05511363	Karuna Therapeutics	Aug 2022	Mar 2025

(Continues)

TABLE 1 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
Lecanemab	DMT, biologic	Aβ	Anti-amyloid monoclonal antibody directed at amyloid protofibrils and amyloid plaques	NCT01760005	Washington University School of Medicine	Dec 2012	Oct 2027
				NCT03887455	Eisai Inc.	Mar 2019	Sep 2027
				NCT04468659	Eisai Inc.	Jul 2020	Oct 2027
				NCT05269394	Washington University School of Medicine	Dec 2021	Jul 2027
Masitinib	DMT, small molecule	Inflammation	Tyrosine kinase inhibitor exhibits neuroprotection via inhibition of mast cell and microglia/macrophage activity	NCT05564169	AB Science	Nov 2022	Nov 2025
Masupirdine	Sx, behavior	Neurotransmitter receptors	5HT6 receptor antagonist	NCT05397639	Suven Life Sciences Limited	Nov 2022	Jan 2025
Metformin	DMT, small molecule	Metabolism and bioenergetics	Insulin sensitizer	NCT04098666	Columbia University	Mar 2021	Mar 2026
Nabilone	Sx, behavior	Neurotransmitter receptors	Synthetic cannabinoid; cannabinoid (receptor agent); antiemetic	NCT04516057	Sunnybrook Health Sciences Centre	Feb 2021	Oct 2025
NE3107	DMT, small molecule	Inflammation	Beta-androstenetriol with anti-inflammatory and insulin signaling effects via ERK 1 and 2	NCT04669028	BioVie Inc.	Aug 2021	Dec 2022
Nilotinib BE	DMT, small molecule	Proteostasis/ proteinopathies	Abl tyrosine kinase inhibitor; autophagy enhancer	NCT05143528	KeifeRx, LLC	Feb 2022	Dec 2025
Omega-3	DMT, small molecule	Oxidative stress	Antioxidant	NCT03691519	University Hospital, Toulouse	Apr 2018	Dec 2023
Piromelatine	DMT, small molecule	Circadian rhythm	Melatonin and serotonin receptor agonist	NCT05267535	Neurim Pharmaceuticals Ltd.	May 2022	May 2024
Remternetug	DMT, biologic	Aβ	Anti-amyloid monoclonal antibody targeting pyroglutamate amyloid	NCT05463731	Eli Lilly and Company	Aug 2022	Mar 2024

(Continues)

TABLE 1 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
Semaglutide	DMT, biologic	Metabolism and bioenergetics	GLP-1 agonist; anti-inflammatory and insulin sensitivity effects	NCT04777396	Novo Nordisk A/S	May 2021	Sep 2025
				NCT04777409	Novo Nordisk A/S	May 2021	Sep 2025
Simufilam (PTI-125)	DMT, small molecule	Synaptic plasticity/neuroprot	Filamin A protein inhibitor; stabilizes the interaction of Aβ42 and the α7 nicotinic acetylcholine receptor to decrease tau phosphorylation and improve synaptic function	NCT04994483	Cassava Sciences, Inc.	Nov 2021	Oct 2023
				NCT05026177	Cassava Sciences, Inc.	Nov 2021	Jun 2024
				NCT05575076	Cassava Sciences, Inc.	Nov 2022	Jul 2026
Solanezumab	DMT, biologic	Aβ	Anti-amyloid monoclonal antibody directed at amyloid monomers	NCT01760005	Washington University School of Medicine	Dec 2012	Oct 2027
				NCT02008357	Eli Lilly and Company	Feb 2014	Dec 2022
Tertomotide	DMT, biologic	Synaptic plasticity/ neuroprotection	Human telomerase reverse transcriptase (hTERT) mimic	NCT05303701	GemVax & Kael	Jan 2023	Oct 2025
Tricaprilin	DMT, small molecule	Metabolism and bioenergetics	Caprylic triglyceride; induces ketosis to provide an alternate energy source to glucose and optimize mitochondrial function	NCT04187547	Cerecin	Jun 2022	Dec 2023
TRx0237	DMT, small molecule	Tau	Tau-aggregation inhibitor	NCT03446001	TauRx Therapeutics Ltd	Jan 2018	Mar 2022
Valiltrami-prosate (ALZ-801)	DMT, small molecule	Aβ	Prodrug of tramiprostate	NCT04770220	Alzheon Inc.	May 2021	May 2024

Abbreviations: Aβ, amyloid beta; CADRO, Common Alzheimer's Disease Research Ontology; cGMP, current good manufacturing practice; DMT, disease-modifying therapy; GLP-1, glucagon-like peptide 1; NCT#, National Clinical Trial number; NMDA, N-methyl-D-aspartic acid; Sx, symptoms.

TABLE 2 Agents in Phase 2 of Alzheimer's disease drug development (ClinicalTrials.gov accessed January 1, 2023).

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
ABBV-916	DMT, biologic	Aβ	Anti-amyloid antibody	NCT05291234	AbbVie	Aug 2022	Dec 2024
ABvac40	DMT, biologic	Aβ	Active immunotherapy (SC injection)	NCT03461276	Araclon Biotech S.L.	Feb 2018	Dec 2021
ACI-24.060	DMT, biologic	Aβ	Vaccine stimulates antibodies against Aβ protein	NCT05462106	AC Immune SA	Jun 2022	Jun 2026
ACI-35	DMT, biologic	Tau	Active immunotherapy targeting tau (phosphorylated tau)	NCT04445831	AC Immune SA	Jul 2019	Oct 2023
AL 001	DMT, small molecule	Synaptic plasticity/ neuroprotection	Lithium inhibits GSL3-beta activating mTOR to facilitate the Akt signaling pathway	NCT05363293	Alzamend Neuro, Inc.	May 2022	Dec 2022
AL002	DMT, biologic	Inflammation	Monoclonal antibody targeting *TREM2* receptors	NCT04592874	Alector Inc.	Jan 2021	Dec 2023
Allopregna-nolone	DMT, small molecule	Neurogenesis	Allosteric modulator of GABA-A receptors	NCT04838301	University of Arizona	Jan 2023	Jan 2025
APH-1105	DMT, small molecule	Aβ	Alpha secretase modulator (amyloid precursor protein secretase modulator)	NCT03806478	Aphios	Jun 2023	Sep 2024
Bacillus Calmette-Guerin	DMT, biologic	Inflammation	Immunomodulation	NCT05004688	Steven E. Arnold	Mar 2022	Oct 2023
Baricitinib	DMT, small molecule	Inflammation	Janus kinase (JAK) inhibitor	NCT05189106	Massachusetts General Hospital	Dec 2022	Jul 2024
Bepranemab	DMT, biologic	Tau	Anti-tau monoclonal antibody binding to central region of tau	NCT04867616	UCB Biopharma SRL	Jun 2021	Apr 2024
BIIB080	DMT, biologic	Tau	Antisense oligonucleotide that inhibits translation of tau mRNA into the tau protein	NCT05399888	Biogen	Aug 2022	Dec 2026
Brain shuttle gantenerumab	DMT, biologic	Aβ	Monoclonal antibody directed at plaques and oligomers; "brain-shuttle" gantenerumab	NCT04639050	Hoffmann-La Roche	Mar 2021	Jan 2025
Bryostatin 1	DMT, biologic	Synaptic plastic-ity/neuroprotection	Protein kinase C inhibitor	NCT04538066	Neurotrope Bioscience, Inc.	Aug 2020	Nov 2022
Buntanetap	DMT, small molecule	Proteostasis/ proteinopathies	Reduce amyloid precursor protein (APP) synthesis; selective inhibitor of APP to reduce amyloid; reduces synthesis of tau and alpha-synuclein proteins	NCT02925650	Annovis Bio Inc.	Mar 2017	Dec 2021

(Continues)

TABLE 2 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
Canakinumab	DMT, biologic	Inflammation	Anti-IL-1-beta monoclonal antibody	NCT04795466	Novartis Pharmaceuticals	Oct 2021	Feb 2026
Chinese traditional medicine	Sx, cognition	Metabolism and bioenergetics	Three herbs (*Rhizoma Acori Tatarinowii*, *Poria cum Radix Pini*, *Radix Polygalae*) mechanism unknown	NCT05538507	Peking Union Medical College Hospital	Jun 2022	Jun 2024
CORT108297	Sx, cognition	Growth factors and hormones	Selective glucocorticoid receptor antagonist	NCT04601038	Johns Hopkins University	Jun 2021	Jun 2023
Crenezumab	DMT, biologic	Aβ	Monoclonal antibody targeting soluble oligomers	NCT01998841	Genentech, Inc.	Dec 2013	Mar 2022
CST-2032	Sx, cognition	Neurotransmitter receptors	Noradrenergic agonist	NCT05104463	CuraSen Therapeutics, Inc.	Apr 2022	Jun 2023
CY6463	DMT, small molecule	Synaptic plasticity/neuroprotection	Guanylate cyclase positive allosteric modulator	NCT04798989	Cyclerion Therapeutics	Jun 2021	Jul 2022
Dalzanemdor	DMT, small molecule	Synaptic plasticity/neuroprotection	Enhances synaptic function through NMDA receptor blockade	NCT05619692	Sage Therapeutics	Feb 2023	Dec 2024
Dapagliflozin	DMT, small molecule	Metabolism and bioenergetics	Sodium-glucose cotransporter 2 (SGLT2) Inhibitor	NCT03801642	Jeff Burns, MD	Jan 2019	Oct 2022
Daratumumab	DMT, biologic	Inflammation	Human antibody targeting CD38; immunomodulatory effects	NCT04070378	Marc L. Gordon, MD	Nov 2019	Dec 2023
Dasatinib + quercetin	DMT, small molecule	Inflammation	Dasatinib induces apoptosis in senescent cells to allow their removal; quercetin is a flavonoid	NCT04063124	The University of Texas Health Science Center at San Antonio	Feb 2020	Dec 2021
				NCT04685590	Wake Forest University Health Sciences	Dec 2021	Jan 2027
				NCT04785300	James L. Kirkland, MD, PhD	Jul 2022	Dec 2023
				NCT05422885	Lew Lipsitz	May 2022	Jun 2023
Deferiprone	DMT, small molecule	Cell death	Iron chelating agent	NCT03234686	Neuroscience Trials Australia	Jan 2018	Sep 2022
DHA	DMT, small molecule	Oxidative stress	Omega 3 fatty acid; reduce amyloid production; improve synaptic function; antioxidant	NCT03613844	University of Southern California	Jul 2018	May 2024
Dronabinol	Sx, behavior	Neurotransmitter receptors	CB1 and CB2 endocannabinoid receptor partial agonist	NCT02792257	Johns Hopkins University	Mar 2017	May 2023
E2814	DMT, biologic	Tau	Anti-tau monoclonal antibody	NCT04971733	Eisai Inc.	Jun 2021	Sep 2024

(Continues)

TABLE 2 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
Edaravone	DMT, small molecule	Oxidative stress	Pyrazolone free-radical scavenger	NCT05323812	Treeway B.V.	Sep 2022	Jan 2024
Edonerpic	DMT, small molecule	Synaptic plasticity/neuroprotection	Neurotrophic agent; activates sigma-1 receptor; enhances microglial clearance of Aβ	NCT04191486	FUJIFILM Toyama Chemical Co., Ltd.	Dec 2019	Feb 2023
Elayta	DMT, small molecule	Synaptic plasticity/ neuroprotection	Sigma 2 receptor antagonist; binds to sigma-2/PGRMC1 receptor and regulates Aβ oligomer-mediated synaptic toxicity	NCT03507790	Cognition Therapeutics	Oct 2018	Sep 2023
				NCT04735536	Cognition Therapeutics	Aug 2020	Mar 2023
				NCT05531656	Cognition Therapeutics	Dec 2022	Aug 2026
EX039	DMT, small molecule	Synaptic plasticity/ neuroprotection	Inhibits D-amino acids oxidate to increase NMDA receptor activity	NCT05413655	Excelsior	Aug 2022	Aug 2024
ExPlas	DMT, biologic	Synaptic plasticity/ neuroprotection	Plasma transfusion from exercise-trained donors	NCT05068830	Norwegian University of Science and Technology	Sep 2021	Sep 2024
Flos gossypii flavonoids	DMT, small molecule	Oxidative stress	Anti-oxidant; anti-inflammatory	NCT05269173	Capital Medical University	Oct 2020	Jun 2024
Fosgonimeton (ATH-1017)	DMT, small molecule	Synaptic plasticity/ neuroprotection	Hepatocyte growth factor (HGF); activates signaling via the HGF/MET receptor system; promotes survival of neurons, enhances hippocampal synaptic plasticity	NCT04886063	Athira Pharma	Jun 2021	Apr 2023
Gantenerumab	DMT, biologic	Aβ	Monoclonal antibody directed at plaques and oligomers	NCT04592341	Hoffmann-La Roche	Nov 2020	Dec 2022
GnRH	DMT, biologic	Growth factors and hormones	Antiaging	NCT04390646	Nelly Pitteloud	Aug 2020	Dec 2023
Hydroxypropyl Beta Cyclodextrin	DMT, biologic	apoE, lipids, and lipoprotein receptors	Modulates cholesterol transportation with secondary effects on amyloid, tau, and oxidative e stress	NCT05607615	Cyclo Therapeutics, Inc.	Sep 2022	Mar 2024
IGC-AD1	Sx, behavior	Neurotransmitter receptors	Cannabinoid	NCT05543681	IGC Pharma LLC	Oct 2022	Aug 2023
Insulin	DMT, biologic	Metabolism and bioenergetics	Decreases glucose resistance; increase insulin signaling in the brain	NCT05006599	Wake Forest University Health Sciences	May 2025	May 2029

(Continues)

TABLE 2 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
Insulin + empagliflozin	DMT, biologic	Metabolism and bioenergetics	SGLT2 inhibitor (empagliflozin) and insulin combination therapy; decrease glucose resistance and increase insulin signaling in the brain	NCT05081219	Wake Forest University Health Sciences	Oct 2021	Oct 2026
IVL3003	Sx, cognition	Neurotransmitter receptors	Cholinesterase inhibitor	NCT05345509	Inventage Lab., Inc.	Apr 2023	Mar 2024
JNJ-63733657	DMT, biologic	Tau	Monoclonal antibody targeted at soluble tau (mid-region of tau)	NCT04619420	Janssen Research & Development, LLC	Jan 2021	Mar 2025
L-Serine	DMT, small molecule	Inflammation	Naturally occurring dietary amino acid; inhibits toxic misfolding	NCT03062449	Aleksandra Stark	Mar 2017	Dec 2022
Lamivudine	DMT, small molecule	Epigenetic regulators	Human immunodeficiency virus nucleoside analog reverse transcriptase inhibitor	NCT04552795	Bess Frost, PhD	Feb 2021	Mar 2023
Lecanemab	DMT, biologic	Aβ	Anti-amyloid monoclonal antibody directed at amyloid protofibrils and amyloid plaques	NCT01767311	Eisai Inc.	Dec 2012	Feb 2025
Lenalidomide	DMT, small molecule	Inflammation	Immunomodulator	NCT04032626	St. Joseph's Hospital and Medical Center, Phoenix	Jul 2020	Sep 2023
Leuprorelin	DMT, small molecule	Growth factors and hormones	Gonadotropin releasing hormone (GnRH) receptor agonist	NCT03649724	Weill Medical College of Cornell University	Nov 2020	Feb 2025
Levetiracetam	DMT, small molecule	Synaptic plasticity/ neuroprotection	SV2A modulator enhancing synaptic plasticity	NCT03489044	University of Oxford	Oct 2018	Dec 2022
				NCT03875638	Beth Israel Deaconess Medical Center	Aug 2019	Aug 2023
				NCT04004702	Walter Reed National Military Medical Center	Jan 2020	Dec 2024
LX1001	DMT, biologic	apoE, lipids, and lipoprotein receptors	Adeno-associated virus (AAV) gene transfer vector expressing the cDNA coding for human *APOE* ε2 directly to the CNS/CSF of *APOE* ε4 homozygotes	NCT03634007	Lexeo Therapeutics	Nov 2019	Apr 2023
LY3372689	DMT, small molecule	Tau	O-GlcNAcase enzyme inhibitor	NCT05063539	Eli Lilly and Company	Sep 2021	May 2024
Memantine	DMT, small molecule	Neurotransmitter receptors	NMDA receptor antagonist	NCT05063851	University of Virginia	Oct 2021	Sep 2024

(Continues)

TABLE 2 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
Methylene Blue	DMT, small molecule	Tau	Tau protein aggregation inhibitor	NCT02380573	The University of Texas Health Science Center at San Antonio	Jul 2015	Apr 2022
MIB-626	DMT, small molecule	Aβ	Sirtuin-nicotinamide adenine dinucleotide stimulator to enhance alpha-secretase	NCT05040321	Brigham and Women's Hospital	Dec 2021	Feb 2024
MK-1942	Sx, cognition	Neurotransmitter receptors	Undisclosed	NCT05602727	Merck Sharp & Dohme LLC	Dec 2022	May 2026
Montelukast	DMT, small molecule	Inflammation	Leukotriene receptor antagonist (LTRA); anti-inflammatory effects	NCT03402503	IntelGenx Corp.	Nov 2018	Oct 2023
MW150	DMT, small molecule	Synaptic plasticity/ neuroprotection	p38 alpha MAPK kinase inhibitor	NCT05194163	Neurokine Therapeutics	May 2022	Aug 2024
NanoLithium NP03	DMT, small molecule	Neurotransmitter receptors	Ion with effects on amyloid, oxidation, and inflammation	NCT05423522	Medesis Pharma SA	May 2022	May 2023
Neflamapimod	DMT, small molecule	Synaptic plasticity/ neuroprotection	Selective p38 MAPK alpha inhibitor	NCT03435861	University Hospital, Toulouse	Oct 2018	Apr 2021
Nicotine	Sx, cognition	Neurotransmitter receptors	Nicotinic acetylcholine receptor agonist	NCT02720445	University of Southern California	Jan 2017	Jul 2023
Obicetrapib	DMT, small molecule	apoE, lipids, and lipoprotein receptors	Cholesteryl ester transfer protein (CETP) inhibitor	NCT05161715	NewAmsterdam Pharma	Jan 2022	Jun 2023
Pegipanermin	DMT, biologic	Inflammation	Neutralizes TNF-alpha	NCT05318976	Inmune Bio, Inc.	Feb 2022	Jun 2023
				NCT05321498	Inmune Bio, Inc.	Sep 2022	Jan 2023
				NCT05522387	Inmune Bio, Inc.	Nov 2022	Dec 2025
Pepinemab	DMT, biologic	Inflammation	Monoclonal antibody directed at semaphorin 4D; reduces inflammatory cytokine release	NCT04381468	Vaccinex Inc.	Jul 2021	Dec 2023
Proleukin	DMT, biologic	Inflammation	IL-2 immunomodulator	NCT05468073	Centre Hospitalier St Anne	Oct 2022	Sep 2025
Rapamycin	DMT, small molecule	Proteostasis/ proteinopathies	Autophagy enhancer; mTOR inhibitor; immunomodulator	NCT04629495	The University of Texas Health Science Center at San Antonio	Aug 2021	Dec 2023
REM0046127	Sx, cognition	Neurotransmitter receptors	Modulates Orai calcium ($Ca2^{+}$) channel activity to normalize neuronal $Ca2^{+}$ homeostasis	NCT05478031	reMYND	Jun 2022	Jun 2023
Sargramostim	DMT, biologic	Inflammation	Hematopoietic growth factor granulocyte macrophage colony stimulating factor; anti-inflammatory	NCT04902703	University of Colorado, Denver	Jun 2022	Jul 2024

(Continues)

TABLE 2 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
SCI-110 (Dronabinol + PEA)	Sx, behavior	Neurotransmitter receptors	Cannibinoid and palmitoylethanolamide (an endocannabinoid)	NCT05239390	The Israeli Medical Center for Alzheimer's	Dec 2021	Jun 2023
Seltorexant	Sx, behavior	Circadian rhythm	Dual orexin receptor antagonist	NCT05307692	Janssen Research & Development, LLC	May 2022	Apr 2023
Semorinemab	DMT, biologic	Tau	Anti-tau monoclonal antibody targeting extracellular tau	NCT03828747	Genentech, Inc.	Jan 2019	Jul 2021
Senicapoc	DMT, small molecule	Inflammation	Calcium-activated potassium channel inhibitor	NCT04804241	University of California, Davis	Mar 2022	Dec 2024
Simufilam	DMT, small molecule	Synaptic plasticity/ neuroprotection	Filamin A protein inhibitor; stabilizes the interaction of Aβ42 and the α7 nicotinic acetylcholine receptor to decrease tau phosphorylation and improve synaptic function	NCT04388254 NCT05352763	Cassava Sciences, Inc. Cassava Sciences, Inc.	Mar 2020 May 2022	Jan 2023 Oct 2025
Sovateltide	DMT, small molecule	Neurogenesis	Endothelin B receptor agonist; augments activity of neuronal progenitor cells, neurovascular repair, and neuroregeneration	NCT04052737	Pharmazz, Inc.	Mar 2018	Nov 2022
Suvorexant	DMT, small molecule	Neurotransmitter receptors	Dual orexin receptor antagonist	NCT04629547	Washington University School of Medicine	May 2022	May 2026
T3D-959	DMT, small molecule	Metabolism and bioenergetics	Dual agonist of peroxisome proliferator activated nuclear receptor delta/gamma (PPARδ/γ); regulates glucose and lipid metabolism	NCT04251182	T3D Therapeutics, Inc.	Mar 2021	Apr 2023
TB006	DMT, biologic	Inflammation	Monoclonal antibody targeting galactose-specific lectin (galectin) 3, a β-galactosidase-binding protein that activates macrophages; anti-inflammatory	NCT05074498 NCT05476783	TrueBinding, Inc. TrueBinding, Inc.	Oct 2021 Sep 2022	Oct 2022 Oct 2024
Tdap	DMT, biologic	Inflammation	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine to stimulate inflammatory protection	NCT05183516	Mindful Diagnostics and Therapeutics, LLC	May 2023	Dec 2023

(Continues)

TABLE 2 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start date	Estimated primary completion date
Telmisartan + perindopril	DMT, small molecule	Vasculature	Angiotensin II receptor blocker, PPAR-gamma agonist (telmisartan); angiotensin converting enzyme inhibitor (perindopril)	NCT02085265	Sunnybrook Health Sciences Centre	Mar 2014	Sep 2023
Tertomotide	DMT, biologic	Synaptic plasticity/neuroprotection	Human telomerase reverse transcriptase (hTERT) mimic	NCT05189210	GemVax & Kael	Oct 2022	Jul 2023
THC-free cannabidiol	Sx, behavior	Neurotransmitter receptors	Cannabinoids	NCT04436081	Eastern Virginia Medical School	Feb 2021	Dec 2022
Trazodone	Sx, cognition	Circadian rhythm	Serotonin reuptake inhibitor	NCT05282550	Johns Hopkins University	Jan 2023	Mar 2027
Trehalose injection	DMT, small molecule	Proteostasis/ proteinopathies	Activates transcription factor EB to increase autophagy	NCT05332678	Neuroscience Trials Australia	Jan 2023	Jan 2025
Valacyclovir	DMT, small molecule	Inflammation	Anti-viral against HSV-1 and −2; reduces vira-related "seeding" of amyloid plaque deposition	NCT03282916	New York State Psychiatric Institute	Feb 2018	Dec 2023
Valiltramiprosate (ALZ-801)	DMT, small molecule	Aβ	Aggregation inhibitor	NCT04693520	Alzheon Inc.	Sep 2020	Jul 2023
Varoglutamstat	DMT, small molecule	Aβ	Glutaminyl cyclase (QC) enzyme inhibitor to reduce production of pyroglutamate Aβ	NCT03919162	Vivoryon Therapeutics N.V.	Nov 2021	May 2023
				NCT04498650	Vivoryon Therapeutics N.V.	Jul 2020	Jan 2024
Yangxue Qingnao pills	DMT, small molecule	Vasculature	Cerebral blood flow enhancer; traditional Chinese herbal medicine	NCT04780399	Dongzhimen Hospital, Beijing	Nov 2021	Mar 2024

Abbreviations: Aβ, amyloid beta; Akt, protein kinase B; *APOE*, apolipoprotein E; CADRO, Common Alzheimer's Disease Research Ontology; CNS, central nervous system; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; HSV, herpes simplex virus; IL, interleukin; MAPK, mitogen-activated protein kinase; mTOR, mammalian target or rapamycin; NCT#, National Clinical Trial number; NMDA, N-methyl-D-aspartic acid; PPAR, peroxisome proliferator-activated receptor; SC, subcutaneous; Sx, symptoms; TNF, tumor necrosis factor.

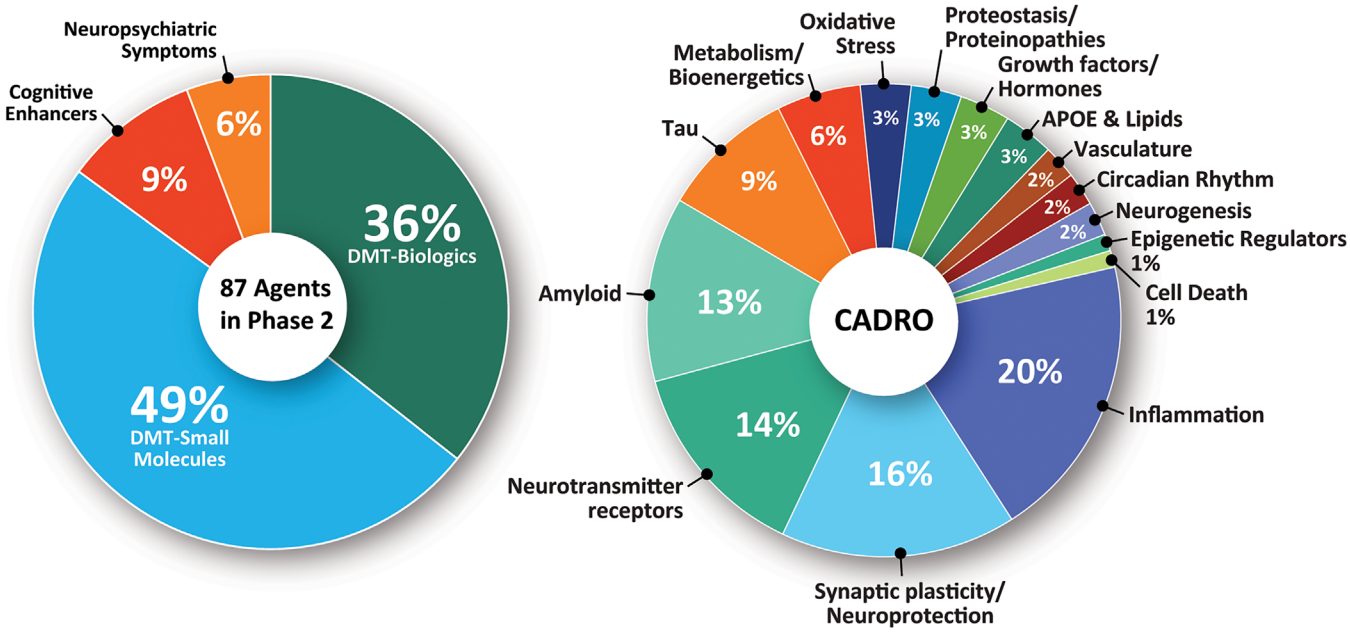

FIGURE 3 Mechanisms of action of agents in Phase 2. *APOE*, apolipoprotein E; DMT, disease-modifying therapy. (Figure © J Cummings; M de la Flor, PhD, Illustrator).

treatments approved for use in another indication (92% = DMT; *N* = 22), 4% (*N* = 1) for cognitive enhancement and 4% (*N* = 1) for treatment for behavioral symptoms. Fourteen trials that were active in 2022 were completed; seven are of unknown status; and one each was suspended, terminated, or withdrawn. Twenty-seven new Phase 2 trials were initiated between January 25, 2022, and January 1, 2023.

Four Phase 2 trials enroll preclinical participants, 30 (30% of Phase 2 trials) trials enroll MCI prodromal participants, 29 (29% of Phase 2 trials) trials enroll early AD participants, 27 (27% of Phase 2 trials) trials enroll mild-to-moderate or moderate AD dementia, 5 (5%) enroll participants with moderate-to-severe and severe AD dementia, and 3 (3%) trials include participants with AD dementia of any severity.

Taken together, currently active trials in Phase 2 trials require a total enrollment of 13,829 participants. DMT trials for biological agents will enroll 5769 participants, trials of small molecule DMTs will enroll 6308 individuals, trials of cognitive enhancing agents will enroll 1282 participants, and trials of drugs being developed for neuropsychiatric syndromes will enroll 470 participants. DMT biological trials have a mean enrollment of 170 participants, DMT small molecule trials have a mean enrollment of 121 participants, trials for cognitive enhancers include a mean of 160 participants, and trials focusing on neuropsychiatric syndromes enroll a mean of 94 participants.

Treatment duration of biologic DMTs in treatment trials for symptomatic AD is 56 weeks and for small molecules in treatments trials is 42 weeks. Treatment exposure in cognitive enhancer trials has a mean of 24 weeks; treatment duration for therapies addressing neuropsychiatric syndromes has a mean exposure period of 8 weeks.

Mean recruitment time for trials of DMT biological agents for symptomatic AD is 104 weeks (on average); recruitment of trials for DMT small molecules took a mean of 125 weeks. Cognitive enhancer trials required a mean recruitment period of 114 weeks. Recruitment for trials of agents addressing behavioral changes in AD had a mean recruitment period of 109 weeks.

3.4 | Phase 1

There are 31 agents in 33 Phase 1 trials (Figure 1, Table 3). There are 25 DMTs (81% of Phase 1 agents) in Phase 1 trials including 16 (52% of the Phase 1 agents) biologics and 9 (29%) small molecules. There are three (10% of Phase 1 agents) putative cognitive enhancing agents and three (10%) drugs targeting behavioral symptoms. CADRO mechanisms represented among Phase 1 therapies include amyloid (7 agents; 23%); inflammation (6 agents; 19%); transmitter receptors (6; 19%); tau (4; 13%); metabolism and bioenergetics (2; 6%); and 1 (3%) each for *APOE* and lipoproteins, neurogenesis, oxidative stress, synaptic plasticity/neuroprotection, and "other." Seven (23%) of the Phase 1 agents are repurposed treatments approved for use in another indication (four DMTs, two cognitive enhancers, one neuropsychiatric agent). Eleven trials that were active in 2022 were completed and seven are of unknown status. Sixteen new Phase 1 trials have been initiated in the past year.

Phase 1 trials include both single ascending dose and multiple ascending dose studies and will enroll 1772 participants into currently registered trials. Most Phase 1 participants are healthy volunteers (*N* = 1165); immunotherapy trials in Phase 1 trial may include

TABLE 3 Agents in Phase 1 of Alzheimer's disease drug development (ClinicalTrials.gov accessed January 1, 2023).

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start Date	Estimated Primary Completion Date
ACU193	DMT, biologic	Aβ	Monoclonal antibody targeting soluble AB oligomers	NCT04931459	Acumen Pharmaceuticals	Jun 2021	Mar 2023
Allopregnanolone	DMT, small molecule	Neurogenesis	Allosteric modulator of GABA-A receptors	NCT03748303	University of Arizona	Oct 2019	Dec 2022
ALN-APP	DMT, biologic	Aβ	RNAi to decrease APP and downstream Aβ-related events	NCT05231785	Alnylam Pharmaceuticals	Feb 2022	Jul 2025
ALZ-101	DMT, biologic	Aβ	Aβ-directed vaccine	NCT05328115	Alzinova AB	Sep 2021	Jul 2023
APNmAb005	DMT, biologic	Tau	Anti-tau antibody	NCT05344989	APRINOIA Therapeutics, LLC	May 2022	Jan 2023
ASN51	DMT, small molecule	Tau	O-GlcNAcase inhibitor	NCT04759365	Asceneuron Pty Ltd.	Jun 2021	Dec 2022
AV-1959	DMT, biologic	Aβ	Anti-amyloid vaccine	NCT05642429	Institute for Molecular Medicine	Feb 2023	Feb 2026
Cannabidiol	Sx, behavior	Neurotransmitter receptors	Cannabinoid	NCT04075435	Mclean Hospital	Jan 2021	Jan 2023
Centella asiatica	DMT, small molecule	Synaptic plasticity/ neuroprotection	Antioxidant and anti-inflammatory agent with synaptic and neuroprotective effects	NCT05591027	Oregon Health and Science University	Nov 2022	Oct 2024
CMS121	DMT, small molecule	Oxidative stress	Fatty acid synthase inhibitor	NCT05318040	Virogenics, Inc.	May 2022	Dec 2022
CpG1018	DMT, biologic	Inflammation	Toll-like receptor 9 agonist leading to reduced Aβ plaques and tau pathology	NCT05606341	NYU Langone Health	Nov 2022	Nov 2024
Donepezil	Sx, cognition	Neurotransmitter receptors	Cholinesterase inhibitor	NCT04730635	Merck Sharp & Dohme LLC	Mar 2021	Jan 2023
Emtricitabine	DMT, small molecule	Inflammation	Nucleoside reverse transcriptase inhibitor (NRTI)	NCT04500847	Butler Hospital	Dec 2021	Mar 2023
GB-5001	Sx, cognition	Neurotransmitter receptors	Cholinesterase inhibitor	NCT05525780	G2GBio, Inc.	Aug 2022	Aug 2023
IBC-Ab002	DMT, biologic	Inflammation	Anti-programmed death-ligand 1 (PD-L1) immune checkpoint inhibitor	NCT05551741	Immunobrain Checkpoint	Oct 2022	Oct 2024
Lecanemab	DMT, biologic	Aβ	Anti-amyloid monoclonal antibody	NCT05533801	Eisai Inc.	Sep 2022	Feb 2023
Lu AF87908	DMT, biologic	Tau	Anti-tau monoclonal antibody	NCT04149860	H. Lundbeck A/S	Sep 2019	Jun 2023

(Continues)

TABLE 3 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial NCT#	Lead sponsor	Start Date	Estimated Primary Completion Date
LX1001	DMT, biologic	apoE, lipids, and lipoprotein receptors	Adeno-associated virus (AAV) gene transfer vector expressing the cDNA coding for human *APOE ε2* directly to the CNS/CSF of *APOE ε4* homozygotes	NCT05400330	Lexeo Therapeutics	Nov 2022	Dec 2027
LY3372993	DMT, biologic	Aβ	Anti-amyloid monoclonal antibody	NCT04451408	Eli Lilly and Company	Jul 2020	Jan 2024
Mecamylamine	Sx, cognition	Neurotransmitter receptors	Nicotinic antagonist	NCT04129060	University of Vermont	Mar 2020	Mar 2024
MK-2214	DMT, biologic	Tau	Anti-tau monoclonal antibody	NCT05466422	Merck Sharp & Dohme LLC	Sep 2022	Nov 2024
MK-8189	Sx, behavior	Neurotransmitter receptors	PDE10 inhibitor	NCT05227118	Merck Sharp & Dohme LLC	Jul 2022	Jan 2023
Nicotinamide riboside	DMT, small molecule	Metabolism and bioenergetics	Mitochondrial function enhancer and antioxidant	NCT04430517	Mclean Hospital	Mar 2022	Apr 2025
NIO752	DMT, biologic	Other	Anti-tau antisense oligonucleotide	NCT05469360	Novartis Pharmaceuticals	Sep 2022	Nov 2023
Psilocybin	Sx, behavior	Neurotransmitter receptors	Psychedelic	NCT04123314	Johns Hopkins University	Mar 2021	Dec 2023
Rapamycin	DMT, small molecule	Proteostasis/ proteinopathies	Autophagy enhancer; mTOR inhibitor; immunomodulator	NCT04200911	The University of Texas Health Science Center at San Antonio	Jun 2020	Jan 2022
Salsalate	DMT, small molecule	Inflammation	Non-steroidal anti-inflammatory (NSAID)	NCT03277573	Adam Boxer	Jul 2017	Apr 2021
SHR-1707	DM, biologic	Aβ	Anti-amyloid monoclonal antibody	NCT04973189	Shanghai Hengrui Pharmaceutical Co., Ltd.	May 2021	Oct 2021
TB006	DMT, biologic	Inflammation	Monoclonal antibody targeting galactose-specific lectin (galectin) 3, a β-galactosidase-binding protein that activates macrophages; anti-inflammatory	NCT04920786	TrueBinding, Inc.	Jun 2021	Nov 2022
Tricaprilin	DMT, small molecule	Metabolism and bioenergetics	Caprylic triglyceride; induces ketosis to provide an alternate energy source to glucose and optimize mitochondrial function	NCT05028114	Cerecin	Aug 2021	Dec 2022
				NCT05408780	Cerecin	Jul 2022	Oct 2022
				NCT05628636	Cerecin	Nov 2022	Feb 2023
VT301	DMT, biologic	Inflammation	Regulatory T cells	NCT05016427	VTBIO Co. LTD	Nov 2020	Nov 2021

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; CADRO, Common Alzheimer's Disease Research Ontology; DMT, disease-modifying therapy; mTOR, mammalian target or rapamycin; NCT#, National Clinical Trial number; Sx, symptoms.

TABLE 4 Stem cell therapy in clinical trials for Alzheimer's disease (ClinicalTrials.gov accessed January 1, 2023).

Agent	Phase	Clinical trial NCT#	Sponsor	Start date	Primary completion date
Allogenic human mesenchymal stem cells	Phase 2	NCT02833792	Stemedica Cell Technologies, Inc.	2016-06-01	2024-07-30
Amniotic and umbilical cord tissue	Phase 1	NCT03899298	R3 Stem Cell	2019-09-01	2024-03-20
Autologous adipose tissue derived mesenchymal stem cells	Phase 2	NCT04482413	Nature Cell Co. Ltd.	2023-02-01	2024-05-30
Human mesenchymal stem cells	Phase 1	NCT04040348	Bernard (Barry) Baumel	2019-10-08	2023-05-01
Human umbilical cord blood derived mesenchymal stem cells	Not applicable	NCT04954534	Samsung Medical Center	2021-07-12	2022-01-31
Lomecel-B (mesenchymal stem cells derived from bone marrow)	Phase 2	NCT05233774	Longeveron Inc.	2021-12-28	2023-09-29
SNK01 (autologous natural killer cells)	Phase 1	NCT04678453	NKGen Biotech, Inc.	2021-01-06	2022-12-01

Abbreviation: NCT#, National Clinical Trial number.

participants with AD of a variety of severities. Trials of biological agents in Phase 1 will require 994 participants, trials of small molecule DMTs will enroll 514 participants, trials of cognitive enhancing agents will enroll 204 participants, and trials of drugs addressing neuropsychiatric syndromes plan to enroll 60 participants. The mean number of participants in DMT biological trials is 62, DMT small molecules will enroll a means of 47 participants, trials of cognitive enhancers enroll a mean of 68 participants, and trials of drugs of neuropsychiatric syndromes will enroll a mean of 20 participants.

Treatment exposure for DMT biologics is 45 weeks and for DMT small molecules is 13 weeks. Treatment duration for cognitive enhancers in Phase 1 is typically 6 weeks; the mean duration for neuropsychiatric agents in Phase 1 is 5 weeks.

Recruitment for Phase 1 DMT trials of biologics averages 65 weeks and for DMT small molecules averages 77 weeks. Cognitive enhancer trials require 113 weeks to recruit and trials for drugs addressing neuropsychiatric symptoms have average recruitment periods of 87 weeks.

3.5 | Stem cells

There are 8 stem cells trials developing cell therapies for AD (Table 4).

3.6 | Biomarkers in trials

Biomarkers are commonly collected at study entry and at study termination. For trials with biomarker descriptions on ClinicalTrials.gov, 72 Phase 2 trials and 34 Phase 3 trials require magnetic resonance imaging (MRI) at baseline. Thirty-one Phase 2 trials and 9 Phase 3 trials collect baseline cerebrospinal fluid (CSF) amyloid; and 29 Phase 2 and 12 Phase 3 collect baseline amyloid positron emission tomography (PET). Plasma amyloid is collected in four Phase 2 and one Phase 3 trial. Tau measures collected at baseline include CSF tau in seven Phase 2 trials and three Phase 3 trials; CSF phospho-tau (p-tau) in six Phase 2 trials and two Phase 3 trials; tau PET in six Phase 2 trials and three Phase 3 trials. Twenty Phase 2 trials and 17 Phase 3 trials do not assess biomarkers at baseline.

MRI is the most common biomarker collected as an outcome measure. MRI data are captured as outcome assessments in 27 Phase 2 trials and 10 Phase 3 trials. Amyloid PET and tau PET are commonly collected as outcomes; amyloid PET in seven Phase 2 and thirteen Phase 3 trials and tau PET in six Phase 2 and nine Phase 3 trials. Amyloid and tau measures are collected in CSF and in plasma are collected as outcomes. Thirteen Phase 2 trials and three Phase 3 trials collect CSF amyloid; fifteen Phase 2 trials and six Phase 3 trials collect CSF tau; eleven Phase 2 trials and five Phase 3 trials collect CSF p-tau. These same three biomarkers are also collected in plasma. Twelve Phase 2 trials and two Phase 3 trials collect plasma amyloid, five Phase 2 trials and one Phase 3 trial collect plasma tau, and eight Phase 2 trials and three Phase 3 trials collect plasma p-tau. A few trials collect neurofilament light (CSF: six Phase 2 trials, three Phase 3 trials; plasma: four Phase 2 trials, four Phase 3 trials) and glial fibrillary acidic protein (GFAP) in CSF and in plasma (CSF: one Phase 2 trial; plasma: one Phase 3 trial). Electroencephalography (EEG) is collected in seven Phase 2 trials and no Phase 3 trials.

3.7 | Trial participants

To fully populate the 187 trials in the pipeline, 57,465 participants are needed. Of these, 41,864 are required for Phase 3 trials; 13,829 for Phase 2 trials; and 1772 for Phase 1 trials. An additional 4632 participants are required for Phase 4 trials or trials with unlabeled phases.

3.8 | Trial sponsors

Of the 187 currently active Phase 1, 2, and 3 trials, 108 (58%) are industry sponsored; 17 (9%) are public–private partnerships; 60 (32%) include the NIH, individuals, universities, advocacy groups, and other organizations; and 2 are funded through other US federal agencies. Industry contributes to 67% of all current clinical trials. Thirty-nine of 55 (71%) Phase 3 trials are industry sponsored, 50 of 99 (51%) Phase 2 trials are sponsored by industry and 19 of 33 (58%) Phase 1 trials are funded through industry. NIH, academic, advocacy, and philanthropic enterprises sponsor 9 of 55 (16%) Phase 3 trials, 41 of 99 (41%) Phase 2 trials, and 10 of 33 (30%) Phase 1 trials.

3.9 | Repurposed agents

Repurposed agents represent 28% (56/187) of clinical trials in the current AD pipeline and 28% (40/141) of drugs in the current pipeline. These agents tend to have their greatest role in Phase 2 proof-of-concept (POC) trials in which they represent 24 of 99 (24%) drugs. Of all repurposed agents, 60% are in Phase 2 (24/40). There are 12 repurposed agents (33%) in Phase 3 and 7 such agents (23%) in Phase 1.

There are seven (18%) repurposed biological agents addressing disease modification in the pipeline. Of repurposed small molecules, 58% (23/40) target disease modification, 13% (5/40) address neuropsychiatric symptoms, and 13% (5/40) target cognitive enhancement.

Funding of repurposed drugs differs markedly from that of the pipeline generally. Seven of 40 (18%) repurposed drugs in the pipeline are funded by industry; 1 is funded through a public–private partnership; and 32 (80%) are funded through NIH, academic, advocacy, and philanthropic enterprises.

3.10 | Global trial distribution

Eighty-three of 187 (44%) trials are conducted in North America only; 42 of 187 (22%) are conducted only outside of North America; and 46 of 187 (25%) are conducted in both North American and non–North American sites (the data are missing for 16 trials). In Phase 3, 14 of 55 (25%) trials are conducted in North America only, 9 of 55 (16%) are conducted outside of North America only, and 28 of 55 (51%) are conducted in both North American and non–North American sites. Forty-nine of 99 (49%) Phase 2 trials used North American sites only, 26 of 99 (26%) used only non–North American sites, and 15 of 99 (15%) used both North American and non–North American sites. Phase 1 trials are conducted primarily in North America (20 of 33; 61%), with a substantial number of Phase 1 trials conducted only in non–North American sites (7 of 33; 21%), and few Phase 1 trials involve both North American and non–North American sites (3 of 33; 9%).

4 | DISCUSSION

Thirty-seven new therapies—22 new chemical entities and 15 biologics—were approved by the FDA in 2022 across all therapeutic categories.[9] Five agents are active in the central nervous system (CNS) including one agent for relapsing multiple sclerosis, one treatment for amyotrophic lateral sclerosis, one anticonvulsant, and one therapy for the treatment of insomnia. One biological agent was directed at cerebral adrenoleukodystrophy to slow the progression of neurologic dysfunction. This is the smallest number of new drugs approved since 2016. There were no new treatments approved for AD in 2022. In 2021 and 2023, respectively, aducanumab and lecanemab received accelerated approval for the treatment of AD. Development for AD continues to be challenging with only these two drugs approved since 2003.

Review of the CADRO categories of disease processes that represent drug targets demonstrates that inflammation, amyloid, neurotransmitter receptors, synaptic plasticity, tau biology, oxidation, and proteostasis/proteinopathy represent the major targets for drug development (Figure 4). Targets related to inflammation comprise one of the largest categories in the pipeline, with 16% ($N = 25$) of agents; in Phase 2, agents addressing inflammatory targets represent 20% of all drugs in development. There has been a consistent number of anti-inflammatory agents in the pipeline over the past few years. In 2020, there were 20 anti-inflammatory agents (16.5%); 2021 had 19 agents (15%); and 2022 had 23 agents (16%). Nearly every anti-inflammatory agent has a different target within the inflammatory cascade (Tables 1–3). Outcomes of the trials may inform which targets can be modulated with therapeutic benefit and what combinations of targets may be desirable.

Other common targets of drugs in the pipeline include amyloid 16%, transmitters 20%, synaptic plasticity and circuits 13%, tau targets 9%, and metabolism and bioenergetics drugs 6% (Figures 2–4). The canonical targets of amyloid and tau comprise 25% of the AD drug development pipeline; the remaining 75% include 14 CADRO categories representing a diverse array of targets among drugs being developed.

Less target diversity is evident in Phase 3 (9 CADRO categories) than Phase 2 (15 categories) reflecting the POC purpose of Phase 2 and the exploration of novel targets at this stage of development. Treatments related to *APOE* are uncommon in the pipeline despite the influential role played by *APOE* ε4 in the biology of AD. Cell death as a drug development target is also uncommon, notwithstanding its role in the amyloid, tau, neurodegeneration (AT[N]) approach to AD pathogenesis and biomarkers. Neurotransmitter receptor agents are well represented in the pipeline in part because cognitive enhancing agents and treatments for neuropsychiatric syndromes address transmitter receptor biology. The large number of target processes being addressed by agents in the pipeline will provide important information regarding which processes represent viable targets for AD drug development. Conclusions about the efficacy demonstrated must be

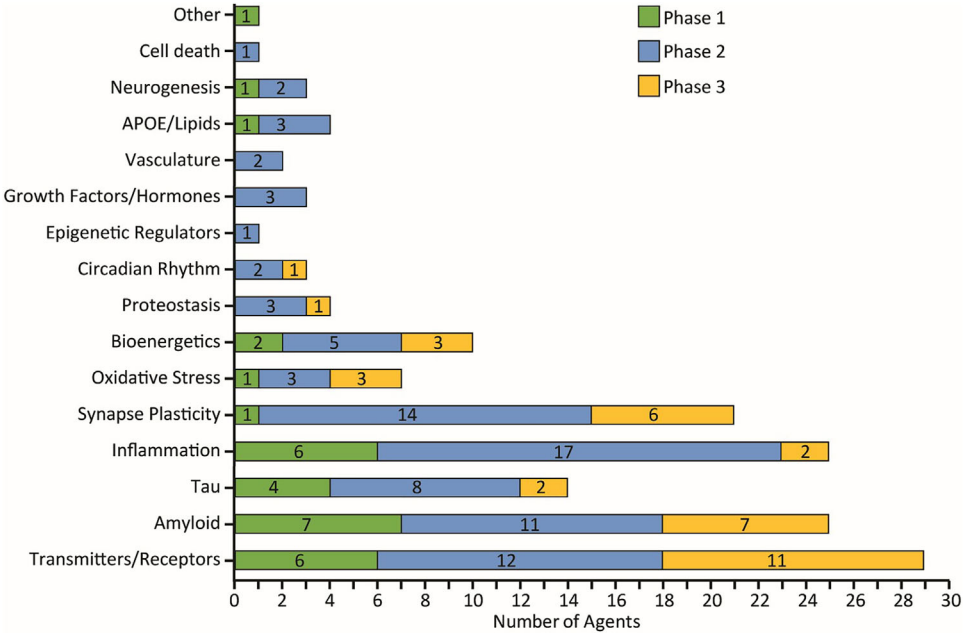

FIGURE 4 Mechanisms of action of all agents in all phases of clinical trials grouped according to the Common Alzheimer's Disease Research Ontology (CADRO). *APOE*, apolipoproein E. (Figure © J Cummings; M de la Flor, PhD, Illustrator).

considered in the context of the features of the trial, including sample size, target exposure, and population assessed.

Repurposed agents represent 33% of Phase 3 agents, 28% of Phase 2 agents, and 23% of Phase 1 agents. These drugs have been approved for another indication and are being explored for their possible utility in the treatment of AD. Most but not all these drugs are generic. Most repurposed agents are studied in Phase 2 POC trials. In the current pipeline, there are 12 repurposed agents in Phase 3, 24 in Phase 2, and 7 in Phase 1. Development programs for repurposed agents are most likely to be funded by academic (in conjunction with the NIH), advocacy, and philanthropic organizations. Eighty percent of repurposed agents are funded through these mechanisms. The disproportionately smaller role played by the biopharmaceutical industry compared to NIH, academics, advocacy, and philanthropic entities in the development of repurposed agents reflects the difficulty of protecting intellectual property for generic drugs that comprise the foundation for marketability and return on investment.[10,11] Deployment and marketing of a successfully developed repurposed compound requires substantial funding. Policy changes, financial incentives, innovation surcharges, and tax advantages will be necessary to attract the funding required to advance repurposed agents to market.[12,13] These policy revisions are needed to allow repurposed agents to move beyond their current value in POC trials and become viable therapies for patients.

The globalization of trials is increasingly evident, especially in large late-stage trials; 51% of Phase 3 trials include both North American and non–North American sites. This reflects the large number of patients and sites required to recruit the large populations required for Phase 3 trials.

Trials increasingly require biological confirmation of the presence of amyloid in participants. Sixty-four Phase 2 trials and 21 Phase 3 trials require CSF amyloid, CSF amyloid/tau ratios, or amyloid PET at entry. A few trials (four Phase 2; one Phase 3) collect plasma amyloid measures at entry. Tau PET is beginning to have a larger role in clinical trials with six Phase 2 and three Phase 3 trials requiring tau imaging documentation at baseline.

The profile of biomarkers collected as trial outcomes differs from that of biomarkers collected at entry. Outcomes of anti-amyloid therapies would require amyloid measures as an outcome; non-amyloid therapeutics might use amyloid for diagnostic confirmation but not as an outcome. There are 20 Phase 2 trials and 16 Phase 3 trials with CSF amyloid or amyloid PET as outcomes. Tau PET is used as an outcome in six Phase 2 trials and nine Phase 3 trials. Biomarkers are playing an increasingly large role in clinical trials in which they may have one or more defined contexts of use including risk determination, diagnosis, monitoring, pharmacodynamic measurement, prognosis determination, response prediction, and safety.[14,15] Use of markers in drug development increases the probability of success and is increasingly viewed as a foundational aspect of clinical trials of DMTs.[16]

Recruitment is a major challenge for AD clinical trials and a key reason for delay in drug development decisions and advancing new therapies to late-stage development and possible approval. A Phase 3 biological agent (for symptomatic participants) has a mean treatment duration of 103 weeks and will require, on average, 147 weeks to recruit the participants; a Phase 3 DMT small molecule with a mean treatment period of 56 weeks will require an average of 99 weeks to recruit. The recruitment challenges are more extreme for symptomatic agents. A trial of a cognitive enhancing agent with a mean

exposure period of 25 weeks will require an average of 142 weeks for recruitment; trials of treatments for neuropsychiatric symptoms with an average treatment period of 19 weeks require a mean of 194 weeks for recruitment.

The AD drug development pipeline is leading to new therapies. After a 17-year hiatus in drug approvals, two agents—aducanumab and lecanemab—have entered the market since 2021; brexpiprazole ameliorated agitation in a Phase 3 AD trial; and suvorexant reduced insomnia in AD in a Phase 3 trial.[17] Aducanumab and lecanemab are the first DMTs for AD and among the first DMTs for any neurodegenerative disease.[18–20] Both agents were approved by the FDA using the accelerated pathway based on the reasonable likelihood that amyloid plaque reduction seen on amyloid PET predicts clinical benefit characterized by the slowing of disease progression.[21] A confirmatory trial to demonstrate the clinical efficacy of aducanumab was required by the FDA and a confirmatory trial for lecanemab has been completed.[20] The success of these agents suggests that the understanding of AD-related biology has progressed sufficiently to allow identification of targets whose modulation ameliorates clinical decline. In addition to improvements in the definition of targets, the availability of more informative biomarkers, identification of candidate drugs with more promising pharmacokinetic and pharmacodynamic characteristics, better definition of appropriate trial populations, and improved trial conduct contributed to the recent successes and provide the foundation for additional productive drug development programs.[22] The recently approved therapies provide treatment for a relatively limited segment (e.g., early AD) of the large and growing AD population. They represent initial steps in the march toward more comprehensive treatments with multiple therapeutic options for those with or at risk for AD.

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CONFLICT OF INTEREST STATEMENT

J.C. 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. J.C. is supported by NIGMS grant P20GM109025. NINDS grant U01NS093334. NIA grant R01AG053798. NIA grant P20AG068053. NIA grant R35AG71476. and the Alzheimer's Disease Drug Discovery Foundation (ADDF). J.C. owns the copyright of the Neuropsychiatric Inventory. G.L. is a full-time employee of Biogen. K.Z. is the CEO of CNS Innovations. Y.Z. and J.F. declare no competing interests. F.C. is supported by the NIA under Award Numbers U01AG073323, R01AG076448, R01AG082211, R01AG066707, 3R01AG066707-01S1, 3R01AG066707-02S1, R56AG074001, and R35AG71476. F.C. declares no other competing interests. Author disclosures are available in thesupporting information.

CONSENT STATEMENT

Not applicable. All data are from an anonymized publicly available clinical trial registry (ClinicalTrials.gov). No individual patient-level data are available on the registry.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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