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REVIEW ARTICLE

Alzheimer's disease drug development pipeline: 2024

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Abstract

INTRODUCTION: New therapies to prevent or delay the onset of symptoms, slow progression, or improve cognitive and behavioral symptoms of Alzheimer's disease (AD) are needed.

METHODS: We interrogated clinicaltrials.gov including all clinical trials assessing pharmaceutical therapies for AD active in on January 1, 2024. We used the Common Alzheimer's Disease Research Ontology (CADRO) to classify the targets of therapies in the pipeline.

RESULTS: There are 164 trials assessing 127 drugs across the 2024 AD pipeline. There were 48 trials in Phase 3 testing 32 drugs, 90 trials in Phase 2 assessing 81 drugs, and 26 trials in Phase 1 testing 25 agents. Of the 164 trials, 34% ($N = 56$) assess disease-modifying biological agents, 41% ($N = 68$) test disease-modifying small molecule drugs, 10% ($N = 17$) evaluate cognitive enhancing agents, and 14% ($N = 23$) test drugs for the treatment of neuropsychiatric symptoms.

DISCUSSION: Compared to the 2023 pipeline, there are fewer trials (164 vs. 187), fewer drugs (127 vs. 141), fewer new chemical entities (88 vs. 101), and a similar number of repurposed agents (39 vs. 40).

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

- In the 2024 Alzheimer's disease drug development pipeline, there are 164 clinical trials assessing 127 drugs.
- The 2024 Alzheimer's disease drug development pipeline has contracted compared to the 2023 Alzheimer pipeline with fewer trials, fewer drugs, and fewer new chemical entities.

- Drugs in the Alzheimer's disease drug development pipeline target a wide array of targets; the most common processes targeted include neurotransmitter receptors, inflammation, amyloid, and synaptic plasticity.
- The total development time for a potential Alzheimer's disease therapy to progress from nonclinical studies to FDA review is approximately 13 years.

1 | INTRODUCTION

Alzheimer's disease (AD) is an age-related disorder increasing from approximately 5% of individuals aged 65–74, 13.1% of people aged 75–84, and 33.3% of people aged 85 or older.[1] The aging of the global population anticipated the current marked increase in individuals with this disorder and forecasts a coming surge of affected persons. Between 2015 and 2050 the percentage of the world's population of people over age 60 will nearly double from 12% to 22%, comprising 2.1 billion individuals.[2] In the United States, 17.3% of the population is age 65 or older and approximately 6.5 million have AD dementia.[1] Mild cognitive impairment (MCI) affects approximately 22% of the over-age 65 group, and AD is the cause of MCI in approximately 50% of cases.[3,4] Roughly 22% of those age 65 or older have preclinical AD (e.g., cognitively normal with evidence of AD pathology in the brain reflected in biomarkers). Preclinical AD is age-related, affecting up to half of persons aged 90 and above.[4] In the United States, Black and Hispanic individuals and persons with lower educational levels are disproportionately affected by AD.[3] The inescapable conclusions to be drawn from these observations are that AD-type pathology is highly prevalent among older individuals, AD increases with age, and the number of individuals progressing to MCI due to AD and dementia due to AD is high. Prevention, treatment, and scalable public health responses are needed.

After almost two decades of intense pharmacologic and drug development efforts during which no new therapies emerged, recent progress has been made in the development and approval of disease-modifying therapies (DMTs) and symptomatic treatments for neuropsychiatric syndromes of AD. Two anti-amyloid monoclonal antibodies (AA-MABS)—aducanumab and lecanemab—that slow the cognitive decline of AD are approved and another—donanemab—is currently under review.[5–7] Brexpiprazole is approved for the treatment of agitation in dementia associated with AD.[8] These successes have been influential for AD therapeutics including demonstrating the ability to slow disease progression through intervention in key pathological processes of AD, establishing biomarkers as a means of diagnosing AD and following therapeutic responses, providing experience with clinical outcome measures in trials of both DMTs and symptomatic agents, and constructing regulatory standards applicable to the development of DMTs and treatments for symptomatic aspects of AD. The preliminary foundation for future clinical trials for AD therapeutics is in place.

The goal of our annual review of the AD drug development pipeline is to note trends in the therapeutic targets, use of clinical outcome measures, role of biomarkers in clinical trials, and drug mechanisms of action (MoA) of agents being tested in current trials. We assess the trial duration, trial population size, and time to recruit trial participants. The information presented in this review is intended to assist those developing drugs to make evidence-based decisions; to help patients, families, and practitioners understand what drugs may be moving through the pipeline toward possible clinical application; and to help clinician-scientists understand the landscape of putative therapeutic interventions for AD.

2 | METHODS

The data on which this review is based are derived from a clinical research registry—clinicaltrials.gov—maintained by the US National Library of Medicine of the National Institutes of Health (NIH). The US Food and Drug Administration (FDA) Amendment Act of 2007 (updated 2017) requires that all clinical trials conducted in the United States be registered on clinicaltrials.gov.[9] Registration on clinicaltrials.gov must occur within 21 days of enrolling the first patient in the trial. The legal requirement for registration applies to trials that have at least one site in the United States, are conducted under an FDA Investigational New Drug (IND) or investigational device exemption, or involve a drug, biological or device that is manufactured in the United States or its territories. Failure to comply with the common rule can result in civil penalties or withholding of grant funding in the case of federally funded clinical trials. The International Committee of Medical Journal Editors (ICMJE) requires registration and inclusion of the registration number (National Clinical Trial [NCT]) with reports of clinical trials submitted for publication. This requirement further encourages trial registration on clinicaltrials.gov when clinical trials are initiated.[10] More trials are conducted in the US than in any other global region, and many trials conducted outside of the United States are registered on clinicaltrials.gov though not legally obliged to do so. As a result, most but not all clinical trials are registered on clinicaltrials.gov; the information on which this report is based can be regarded as comprehensive but not exhaustive regarding therapeutic agents in clinical trials.

Data are structured in the clinicaltrials.gov Application Programming Interface (API) and transferred to the database of the Clinical Trial Observatory for analysis and interpretation (regularly updated summary data are available at Alzpipeline.com).

The Index Date for this review is January 1, 2024. Numbers, percentages, and other numerical data provided in this report are true regarding clinical trials on the Index Date. Trials reaching their

completion date prior to the Index Date or not yet registered on the Index Date are not included in the review. We include 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 limited to those participating in the double-blind portion of the trials), and not yet recruiting (e.g., registered on clincaltrials.gov but no patients have been enrolled). We note whether trials registered on clinicaltrials.gov on the Index Date are labeled as suspended, terminated, completed, withdrawn, or unknown (no status update within the past 2 years). These latter categories of trials are not included in the calculations involving active trials.

We search to include all trials with labels of AD or other terms related to AD (e.g., dementia of the Alzheimer's type) and MCI. Search algorithms allow trials with spelling or grammatical errors to be detected. We do not include trials whose participants have dementia of any cause or in which AD is included with other dementias or other medical conditions not separately identified by inclusion and exclusion criteria. We do not include trials in which the MCI is a manifestation of a non-AD condition such as MCI of Parkinson's disease.

We include trials in Phase 1, Phase 1/2, Phase 2, Phase 2/3, and Phase 3. When a trial spans two phases, we use the higher number for our calculations. We do not include Phase 0 or Phase 4 clinical trials in this report.

The data resource constructed from the clinicaltrials.gov API is comprehensive and includes the test agent, trial title, NCT number, start date, projected primary end date, duration of treatment exposure, number of arms of the study, whether a biomarker was collected at entry or as an outcome, whether the agent was repurposed (e.g., approved for another indication), whether the trial was a long-term extension of an earlier clinical trial, and where the trials were performed (United States; ex-United States with no US sites; global – US and ex-US sites included in the trial). We calculate the recruitment period as the total trial duration (from the actual start date to the primary completion date) minus the treatment duration.

We use the "lead sponsor" designation derived from clinicaltrials.gov to divide the funders into industry or not industry. Most AD trials not funded by industry are funded by the National Institute on Aging (NIA); trials are also funded by other federal agencies such as the Veterans Administration, non-US governmental agencies, advocacy groups, or philanthropy. Detailed information for public-private partnerships is not available in the registry.

We note if the trial population is cognitively normal with a biomarker indicative of AD (e.g., a prevention trial), MCI, or mild, moderate, or severe AD dementia. If other trial designations are used such as "early AD" (MCI plus mild AD dementia), we capture the population definition.

We derive the target of the test agent based on the descriptive categories of the Common Alzheimer's Disease Research Ontology (CADRO).[11] CADRO categories include amyloid beta; tau; apolipoprotein E (ApoE), lipids, and lipoprotein receptors; transmitter 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; environmental factors; epigenetic regulators; multitarget; unknown target; other. Within each of the CADRO categories, such as synaptic plasticity or inflammation, agents can have one or several specific MoAs. The MoAs presented in the tables are derived from clinicaltrials.gov, available literature, or informational websites such as alzforum.org. Based on MoA information, we classify agents as DMTs or as symptomatic therapies depending on whether the declared therapeutic purpose is to slow cognitive decline or to improve symptoms present at baseline in the trial (cognitive impairment or neuropsychiatric symptoms). We acknowledge that this classification can be ambiguous; agents may have multiple therapeutic mechanisms; and drugs may have both DMT and symptomatic properties. Trials are typically designed to show one therapeutic property of a drug; trials for symptomatic agents are smaller, shorter in duration, and have less reliance on biomarkers, whereas demonstrating disease modification typically requires larger numbers of participants, longer exposures, and more reliance on biomarkers. Trial features

RESEARCH IN CONTEXT

1. **Systemic review**: All clinical trials performed in the United States must be registered on clinicaltrials.gov and most clinical trials conducted globally are entered in this registry. We used this registry to assess the size, duration, and funding of clinical trials for therapies for Alzheimer's disease (AD). We report the therapeutic purpose of the agent, mechanism of action, and biological targets of the agents being assessed.
2. **Interpretation**: The number of trials for AD therapeutics and the number of drugs being assessed is somewhat reduced in the 2024 pipeline compared to the 2023 pipeline. There are similar numbers of repurposed agents and fewer new chemical entities in the 2024 pipeline. There are 96 disease-modifying agents and 31 symptomatic agents in the AD pipeline. The distribution of therapeutic targets as defined by the Common Alzheimer's Disease Research Ontology (CADRO) is diverse with an emphasis on inflammation, synaptic plasticity, transmitter effects, and amyloid ß-protein.
3. **Future directions**: The decrease in the number of trials, drugs, and new chemical entities in the 2024 pipeline suggests that recent successes in the development of disease-modifying therapies and treatments for neuropsychiatric symptoms is not increasing AD pipeline activity. The greater use of biomarkers, refined target identification, and improved trial conduct may increase the number of successes in AD drug development and attract greater interest and investment in this area where new therapies are urgently needed.

are used to classify drugs as DMTs or symptomatic agents. We divide 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 if a drug in the AD pipeline is repurposed, we compare the agents in the pipeline to the currently available version of DrugBank (https://go.drugbank.com/). Most, but not all repurposed agents, are generic. A few in the pipeline such as brexpiprazole are repurposed agents with proprietary status.

In this report, we do not include trials of non-pharmacologic therapeutic approaches such as exercise trials, lifestyle interventions, cognitive behavior therapies, caregiver interventions, supplements, medical foods, or devices. We do not include biomarker trials if no intervention is being assessed.

3 | RESULTS

3.1 | Overview

On the Index Date of January 1, 2024, there were 164 clinical trials for AD (prevention, MCI, AD dementia) assessing 127 drugs. This included 48 trials testing 32 drugs in Phase 3; 90 trials assessing 81 drugs in Phase 2; and 26 trials testing 25 drugs in Phase 1 (Figure 1). Of the 164 trials, 11 are long-term extensions of agents in prior trials.

Most of the drugs in the AD drug development pipeline are DMTs. In total there are 96 DMTs representing 76% of drugs in clinical trials. Twelve percent of the pipeline (15 agents) target cognitive enhancement as their therapeutic purpose, and 13% (16 agents) are proposed treatments for neuropsychiatric symptoms.

Of the 96 disease-modifying agents, 53 (55%) are small molecules and 43 (45%) are biologics. Sixty-six percent (21 agents) in Phase 3 are DMTS; 78% (63 agents) in Phase 2 are DMTs; 84% (21 agents) in Phase 1 are DMTs.

Agents in the pipeline address nearly all the processes of the CADRO classification (Figure 2). Twenty-eight drugs (22% of all drugs in the pipeline) target neurotransmitter receptors; 25 agents (20%) target neuroinflammation; 23 therapies (18%) target amyloid beta protein (Aß) processes; 15 drugs (12%) address synaptic plasticity/neuroprotection; 11 agents (9%) target tau-related processes; 8 agents (6%) address metabolism and bioenergetics; 5 (4%) drugs target *ApoE*, lipids, and lipoprotein receptors; 4 drugs (3%) each address proteostasis/proteinopathy and growth factors and hormones; 3 therapies (2%) target oxidative stress, neurogenesis, and circadian rhythm disturbances; 2 drugs (2%) target vasculature factors; and there is 1 agent (1%) for each of the categories of gut-brain axis and epigenetic regulators.

Of the 164 current AD trials, 35 (21%) are new since the last Index Date (January 1, 2023) including 9 trials in Phase 3, 17 trials in Phase 2, and 9 trials in Phase 1. In the past year, 37 clinical trials were completed, 10 were terminated, 4 were withdrawn, 1 was suspended, and 7 became of "unknown" status.

There are 39 repurposed agents in 52 trials in the pipeline comprising 31% of current drugs and 32% of current trials. Among repurposed agents, 15% (6 agents) are DMT biologics, 54% (21 agents) are DMT small molecules, 15% (6 agents) target cognitive enhancement, and 15% (6 drugs) are being assessed for the treatment of neuropsychiatric symptoms. Repurposed agents account for 14% of DMT biologics, 40% of DMT small molecules, 40% of cognitive enhancing agents, and 38% of neuropsychiatric agents in the pipeline.

Currently active trials require 51,398 participants including 36,998 in Phase 3; 13,138 in Phase 2; and 1,262 in Phase 1. DMTs account of 79% of all participants required for current trials. Forty-four percent of all trials are conducted in the United States without non-US sites. Four trials in the pipeline are prevention trials of cognitively normal individuals at risk for symptomatic AD; 26% of trials (42) are assessing participants with MCI (with or without confirmation of AD pathology); 30% (49 trials) involve participants with early AD (MCI or mild AD dementia); and 75 trials (46%) include participants with mild, moderate, or severe AD dementia.

The pharmaceutical industry accounts for funding of 60% (98 of 164) of trials.

3.2 | Phase 3 trials

There are 48 Phase 3 trials assessing 32 drugs (Table 1; Figure 3). Sixty-six percent of agents ($N = 21$) in Phase 3 are DMTs including nine biologics (43% of DMTs) and 12 small molecules (57%). There are four (12% of Phase 3 agents) cognitive enhancing agents and seven (22% of Phase 3 agents) neuropsychiatric agents in Phase 3. There are nine new trials assessing eight drugs since the Index Date of January 1, 2023. There are nine (28% of Phase 3 agents) repurposed agents in Phase 3; four (44%) of repurposed agents are DMTs (one biologic [25% of repurposed DMTs]; three small molecules [75% of repurposed DMTs]), three (33% of Phase 3 repurposed agents) cognitive enhancing agents, and two (22% of Phase 3 repurposed agents) drugs addressing neuropsychiatric symptoms. Five trials are long-term extensions of drugs that have completed a prior trial. There are two prevention trials in Phase 3 enrolling individuals who are cognitively normal and at risk for progressing to symptomatic AD.

The CADRO categories of agents in Phase 3 include 11 (34%) targeting transmitter systems; 7 (22%) targeting amyloid-related processes; 4 (12%) addressing synaptic plasticity/neuroprotection; 2 (6%) each addressing metabolic and bioenergetic targets, inflammation, and proteostatsis/proteinopathy; and 1 (3%) each directed at tau, neurogenesis, growth factors and hormones, and circadian rhythm-related processes. In total, 10 biological process categories are being addressed by agents in Phase 3 trials.

Thirty-eight trials in Phase 3 (79%) are funded by biopharmaceutical industry sponsors. Twenty-one percent are funded primarily through non-pharmaceutical sources including the NIH (especially the NIA), other federal agencies, non-US governmental agencies, philanthropies (e.g., Alzheimer's Drug Discovery Foundation), and advocacy groups (e.g., Alzheimer's Association). Pharmaceutical/non-pharmaceutical

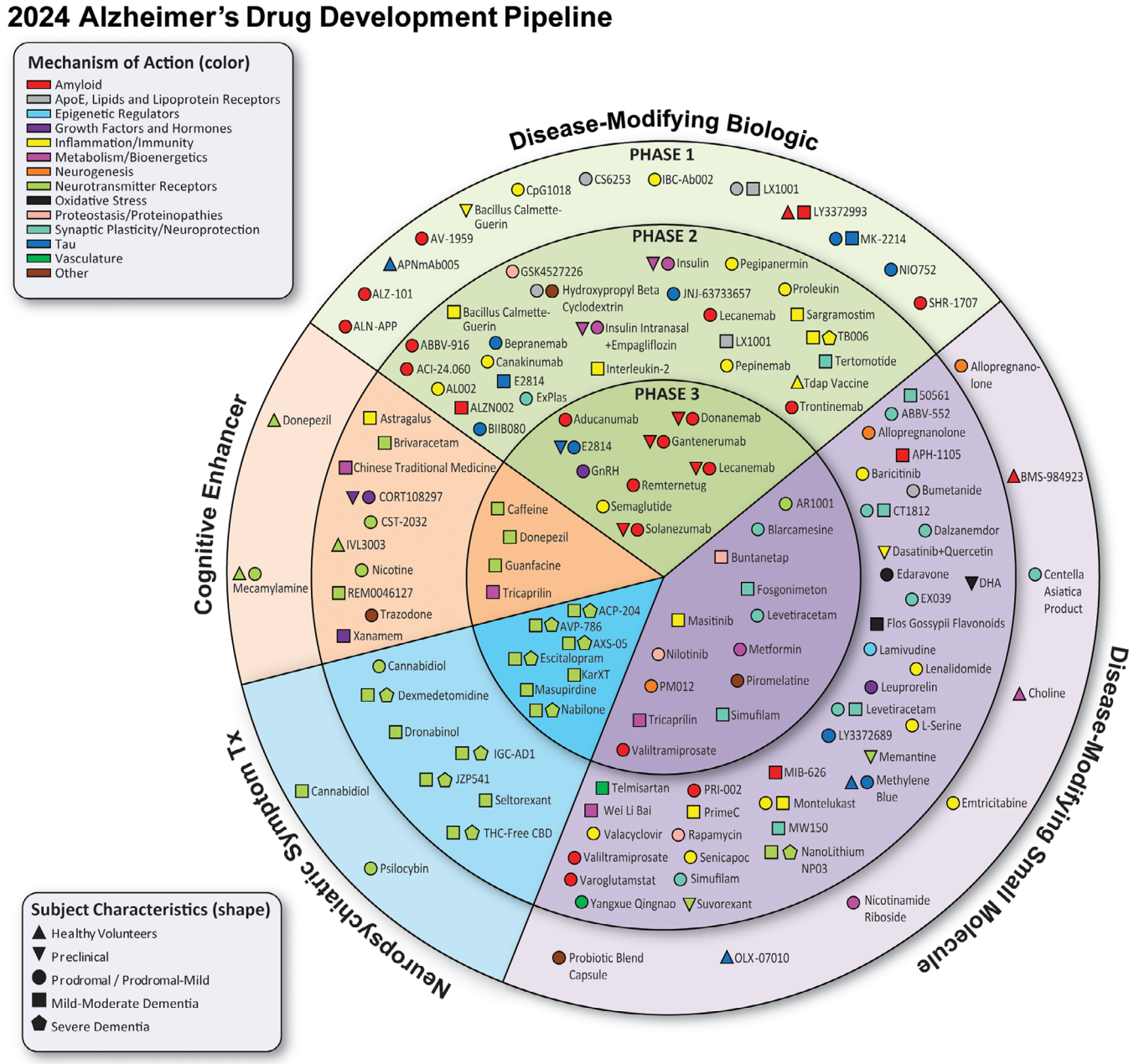

FIGURE 1 Agents in clinical trials for treatment of Alzheimer's disease on the Index Date of January 1, 2024, as recorded on clinicaltrials.gov. The inner ring shows Phase 3 agents; the middle ring includes Phase 2 agents; the outer ring presents Phase 1 therapies. Agents in green areas are biologics; those in purple areas are disease-modifying small molecules; agents in orange areas are symptomatic agents addressing cognitive enhancement; and those in the blue sections of the figure target behavioral and neuropsychiatric symptoms. The shape of the icon denotes the population of the trial; the color of the icon denotes the CADRO-based class of the agent (© J Cummings; M de la Fleur, PhD, Illustrator).

collaborations are common; the API of clinicaltrials.gov does not allow specific identification of public-private partnerships.

There are two Phase 3 prevention trials, both involving biological agents. The mean anticipated recruitment time for prevention trials is 2.9 years. On average, DMT Phase 3 trials (not including prevention trials) of biologics will require 3.5 years and small molecules will require 2.2 years to recruit the needed number of patients. Recruitment for cognitive enhancers takes on average 3.4 years and for trials of neuropsychiatric symptoms, 3.7 years. Treatment duration varies by therapeutic class, Phase 3 prevention trials of biologics have mean treatment periods of 3.8 years. Non-prevention, Phase 3 trials of biologics have a mean treatment period of 1.5 years; non-prevention Phase 3 trials of small molecules have a mean period of 1 year. On average, cognitive enhancer treatment exposure periods and treatment periods of drugs for neuropsychiatric agents in Phase 3 are 4.5 and 4.8 months, respectively.

Phase 3 trials required a total of 36,998 participants to populate all trials currently in progress. DMT biologics have a total of 18,232

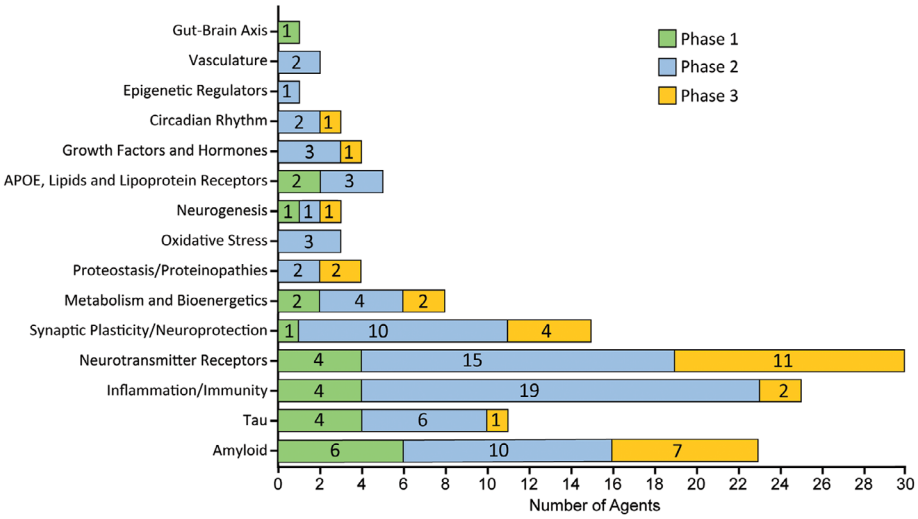

FIGURE 2 Alzheimer-related processes as categorized by the Common Alzheimer's Disease Research Ontology (CADRO) for agents in each phase of the Alzheimer's drug development pipeline (© J Cummings; M de la Flor, PhD, Illustrator).

participants; DMT small molecules have, in total, 10,439 participants; trials of cognitive enhancers require 1,383 participants, and trials of agents for neuropsychiatric symptoms require 6,944 participants. The mean number of participants per trial in Phase 3 trials is 1215.5 for DMT biologic trials, 695.9 for DMT small molecules, 276.6 for cognitive enhancers, and 534.2 for trials of neuropsychiatric agents.

3.3 | Phase 2 trials

There are 90 Phase 2 trials assessing 81 drugs (Table 2; Figure 4). Seventy-eight percent of agents ($N = 63$) in Phase 2 are DMTs including 26 biologics (41% of DMTs) and 37 small molecules (59% of DMTs). There are 10 (12%) cognitive enhancing agents and 8 (10%) neuropsychiatric agents in Phase 2. There are 17 new trials in Phase 2 assessing 17 drugs since the Index Date of January 1, 2023. There are 33 Phase 2 trials assessing repurposed 28 agents and representing 35% of the Phase 2 pipeline. Twenty-two (79%) of repurposed agents are DMTs (5 biologics (23% of DMTs); 17 small molecules (77% of DMTs)); 2 (7% of Phase 2 repurposed agents) cognitive enhancing agents, and 4 (14% of Phase 2 repurposed agents) drugs addressing neuropsychiatric symptoms. Five trials are long-term extensions of trials of drugs that have completed the double bind phase of a prior trial. There is one prevention trial in Phase 2.

The CADRO categories of agents in Phase 2 include 19 (23% of Phase 2 agents) agents addressing inflammation; 15 (19%) agents target transmitter receptors; 10 drugs (12%) target synaptic plasticity/neuroprotection; 10 (12%) target amyloid-related processes; 6 (7%) have tau targets; 4 (5%) have metabolic and bioenergetic targets; 3 (4%) address ApoE and lipids, oxidative stress, or growth factors and hormones; 2 (2%) target proteostasis/proteinopathies, vasculature, and circadian rhythm each; 1 (1%) each address neurogenesis and epigenetic regulators. Fourteen biological process categories are being addressed by agents in Phase 2 trials.

Together all Phase 2 trials require 13,138 participants. Phase 2 DMT trials require 5286 and 5751 for biologic and small molecule studies, respectively. Current cognitive enhancer trials require 1185 participants and trials of drugs for neuropsychiatric symptoms require 916 participants. The mean number of participants for Phase 2 DMT biological agents is 188.8 and for DMT small molecule trials, 130.7. There are an average of 118.5 participants in Phase 2 cognitive enhancer trials and 114.5 participants in Phase 2 trials of neuropsychiatric agents.

Forty-six trials in Phase 2 (51%) are funded by biopharmaceutical industry sponsors with the other 49% funded by a variety of NIH, US federal, non-US governmental, advocacy, and philanthropic non-industry organizations.

On average, DMT Phase 2 trials (not prevention) of biologics and small molecules will each require 2.3 years to recruit the needed number of patients. Recruitment for cognitive enhancers and neuropsychiatric agents will take on average 2.6 years and 2.8 years, respectively. Treatment duration varies by therapeutic class. Non-prevention, Phase 2 trials of biologics have a mean treatment period of 1.2 years; non-prevention, Phase 2 trials of small molecules have a mean period of 0.8 year (10 months). On average, cognitive enhancer treatment exposure periods in Phase 2 trials are 5.9 months and for trials of neuropsychiatric agents, 2.5 months.

3.4 | Phase 1 trials

There are 26 Phase 1 trials assessing 25 drugs (Table 3). Eighty-four percent of agents ($N = 21$) in Phase 1 are DMTs including 13 biologics (62% of DMTs) and eight small molecules (38%). There are two (8% of Phase 1 drugs) cognitive enhancing agents and two (8% of Phase 1 drugs) neuropsychiatric agents in Phase 1. There are nine new trials assessing eight drugs since the Index Date of January 1, 2023.

The CADRO categories of agents in Phase 1 include six (24% of the Phase 1 pipeline) for amyloid; four (16%) each for transmitter

TABLE 1 Agents in Phase 3 Alzheimer's disease drug development (clinicaltrials.gov accessed January 1, 2024).

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start Date	Estimated primary completion date
ACP-204	Neuropsychiatric symptom	Neurotransmitter Receptors	Selective antagonist/inverse agonist of 5-hydroxytryptamine (serotonin) receptor subtype 2A	NCT06159673	ACADIA Pharmaceuticals Inc.	Nov 2023	Jan 2028
Aducanumab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody directed at plaques and oligomers	NCT04241068 NCT05310071	Biogen Biogen	Mar 2020 Jun 2022	Aug 2023 Dec 2025
AR1001	Disease-modifying small molecule	Neurotransmitter receptors	PDE5 inhibitor that reduces amyloid production and decreases inflammation in animal models of AD	NCT05531526	AriBio Co., Ltd.	Dec 2022	Dec 2025
AVP-786	Neuropsychiatric symptom	Neurotransmitter receptors	NMDA receptor antagonist, sigma 1 receptor agonist; serotonin and norepinephrine transporter inhibitor	NCT02446132 NCT03393520 NCT04408755 NCT04464564	Otsuka Pharmaceutical Development & Commercialization, Inc.	Dec 2015 Oct 2017 Jul 2020 Sep 2020	Jul 2025 Dec 2023 Dec 2024 Dec 2024
AXS-05	Neuropsychiatric symptom	Neurotransmitter receptors	NMDA receptor antagonist, sigma 1 receptor agonist; serotonin and norepinephrine transporter inhibitor	NCT04947553 NCT05557409	Axsome Therapeutics, Inc.	Jun 2021 Sep 2022	Jun 2023 Jun 2025
Blarcamesine	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	Sigma-1 receptor agonist, M2 autoreceptor antagonist	NCT04314934	Anavex Life Sciences Corp.	Oct 2019	Jul 2024
Buntanetap	Disease-modifying small molecule	Proteostasis/ proteinopathies	Decrease protein translation	NCT05686044	Annovis Bio Inc.	Apr 2023	Feb 2024
Caffeine	Cognitive enhancement	Neurotransmitter receptors	Adenosine antagonist; non-specific phosphodiesterase inhibitor	NCT04570085	University Hospital, Lille	Mar 2021	Nov 2024
Donanemab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody specific for pyroglutamate plaque amyloid	NCT04437511 NCT05026866 NCT05508789 NCT05738486	Eli Lilly and Company	Jun 2020 Aug 2021 Oct 2022 Feb 2023	Apr 2023 Oct 2027 Apr 2027 Mar 2024
Donepezil	Cognitive enhancement	Neurotransmitter receptors	Acetylcholinesterase inhibitor; adipokine modulation	NCT04661280 NCT05592678	Assistance Publique—Hôpitaux de Paris The University of Texas Health Science Center at San Antonio	Feb 2022 Mar 2024	Aug 2026 Nov 2028
E2814	Disease-modifying biologic	Tau	Anti-tau monoclonal antibody	NCT01760005 NCT05269394	Washington University School of Medicine	Dec 2012 Dec 2021	Oct 2027 Jul 2027
Escitalopram	Neuropsychiatric symptom	Neurotransmitter receptors	Selective serotonin reuptake inhibitor	NCT03108846	JHSPH Center for Clinical Trials	Jan 2018	May 2024

(Continues)

TABLE 1 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start Date	Estimated primary completion date
Fosgonimeton	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	Hepatocyte growth factor (HGF); activates signaling via the hepatocyte growth factor (HGF)/MET receptor system; promotes survival of neurons, enhances hippocampal synaptic plasticity	NCT04488419 NCT04886063	Athira Pharma	Sep 2020 Jun 2021	Jul 2024 Jan 2027
Gantenerumab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody	NCT01760005	Washington University School of Medicine	Dec 2012	Oct 2027
GnRH	Disease-modifying biologic	Growth factors and hormones	Anti-aging	NCT04390646	Nelly Pitteloud	Aug 2020	Dec 2028
Guanfacine	Cognitive enhancement	Neurotransmitter receptors	Alpha-2 adrenergic agonist	NCT03116126	Imperial College London	Jan 2019	Dec 2022
KarXT	Neuropsychiatric symptom	Neurotransmitter receptors	Muscarinic cholinergic agonist with peripheral anticholinergic	NCT05511363 NCT05980949 NCT06126224	Karuna Therapeutics	Aug 2022 Jul 2023 Dec 2023	Mar 2025 Apr 2026 Jul 2025
Lecanemab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody directed at amyloid protofibrils and amyloid plaques	NCT01760005 NCT03887455 NCT04468659 NCT05269394	Washington University School of Medicine Eisai Inc. Eisai Inc. Washington University School of Medicine	Dec 2012 Mar 2019 Jul 2020 Dec 2021	Oct 2027 Sep 2027 Oct 2027 Jul 2027
Levetiracetam	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	Modulator of the synaptic vesicle protein (SV2A) to reduce aberrant neuronal hyperactivity	NCT05986721	AgeneBio	Dec 2024	Jul 2028
Masitinib	Disease-modifying small molecule	Inflammation	Tyrosine kinase inhibitor; exhibits neuroprotection via inhibition of mast cell and microglia/macrophage activity	NCT05564169	AB Science	Jan 2024	Dec 2026
Masupirdine	Neuropsychiatric symptom	Neurotransmitter receptors	5HT6 receptor antagonist	NCT05397639	Suven Life Sciences Limited	Nov 2022	Jan 2025
Metformin	Disease-modifying small molecule	Metabolism and bioenergetics	Insulin sensitizer	NCT04098666	Columbia University	Mar 2021	Mar 2026
Nabilone	Neuropsychiatric symptom	Neurotransmitter receptors	Synthetic cannabinoid; cannabinoid (receptor agent); antiemetic	NCT04516057	Sunnybrook Health Sciences Center	Feb 2021	Oct 2025

(Continues)

TABLE 1 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start Date	Estimated primary completion date
Nilotinib BE	Disease-modifying small molecule	Proteostasis/ Proteinopathies	Abl tyrosine kinase inhibitor; autophagy enhancer	NCT05143528	KeifeRx, LLC	Feb 2022	Dec 2025
Piromelatine	Disease-modifying small molecule	Circadian rhythm	Melatonin and serotonin receptor agonist	NCT05267535	Neurim Pharmaceuticals Ltd.	May 2022	May 2024
PM012	Disease-modifying small molecule	Neurogenesis	Upregulation of BDNF	NCT05811000	Mediforum Ltd., Co.	Nov 2020	Feb 2021
Remternetug	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody	NCT05463731	Eli Lilly and Company	Aug 2022	Oct 2025
Semaglutide	Disease-modifying biologic	Inflammation	GLP-1 agonist; anti-inflammatory and insulin sensitivity effects	NCT04777396 NCT04777409 NCT05891496	Novo Nordisk A/S	May 2021 May 2021 Jun 2023	Sep 2025 Sep 2025 May 2024
Simufilam	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	Filamin A conformation stabilizer; disrupts the interaction of filamin A with the alpha 7 nicotinic acetylcholine receptor to reduce tau hyperphosphorylation and neurodegeneration; dependent on A-beta's signaling via the alpha 7 pathway	NCT04994483 NCT05026177 NCT05575076	Cassava Sciences, Inc.	Nov 2021 Nov 2021 Nov 2022	Oct 2024 May 2025 Jul 2026
Solanezumab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody	NCT01760005	Washington University School of Medicine	Dec 2012	Oct 2027
Tricaprilin	Cognitive enhancement	Metabolism and bioenergetics	Caprylic acid is metabolized to ketone bodies to create ketosis and stimulate mitochondria	NCT05809908	Cerecin	Jan 2024	Jan 2026
Valiltramiprosate	Disease-modifying small molecule	Amyloid beta	Prodrug of tramiprostate	NCT04770220	Alzheon Inc.	May 2021	May 2024

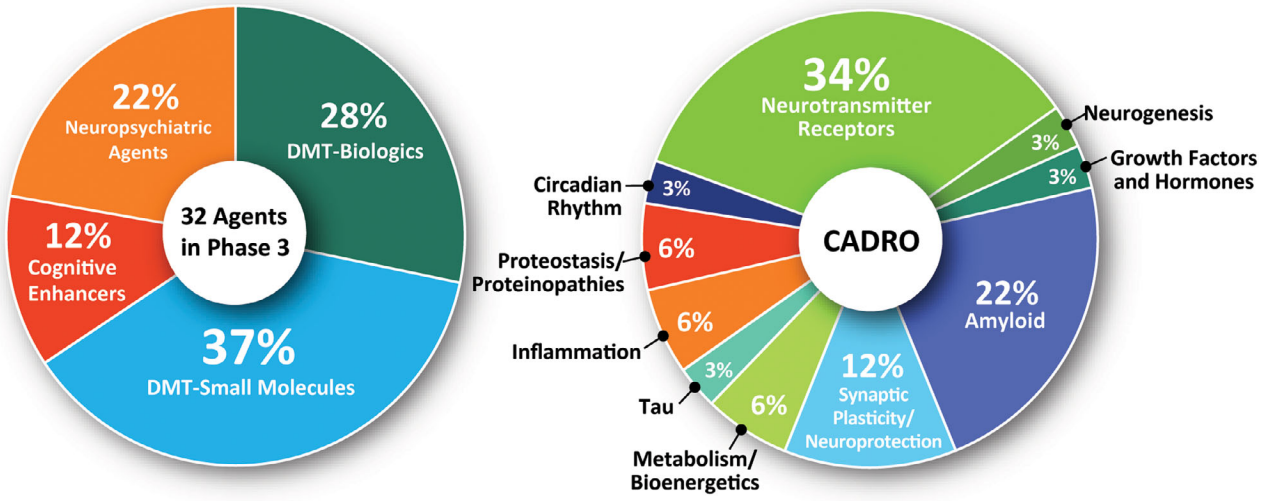

FIGURE 3 Mechanisms of action of agents in Phase 3 Alzheimer clinical trials as classified using 4 categories of therapeutic purpose (left) or the Common Alzheimer's Disease Research Ontology (CADRO) approach (right)(figure © J Cummings; M de la Flor, PhD, Illustrator).

receptors, tau, and inflammation; two (8%) each for ApoE/lipids and metabolism and bioenergetics; and one (4%) each for neurogenesis, synaptic plasticity/neuroprotection, and gut-brain axis. Nine CADRO processes are included among the targets of Phase 1 compounds.

Fourteen (54%) Phase 1 trials are funded by biopharmaceutical industry sponsors.

Phase 1 trials require 1,262 participants for all ongoing trials. DMT trials will enroll 1054 participants, 705 for biologics and 349 for small molecules. Phase 1 cognitive enhancer trials require 176 participants, and trials of drugs for neuropsychiatric symptoms require 32 participants. DMT biologic trials have a mean of 54 participants; DMT small molecules have, on average, 39 participants; trials of cognitive enhancers have a mean trial size of 88 participants; and trials of agents for neuropsychiatric symptoms include 16 participants.

On average, DMT Phase 1 trials of biologics will require 1.5 years and small molecules will require 1.7 years to recruit the needed number of patients. Recruitment for cognitive enhancers and neuropsychiatric agents takes on average 2.2 and 3.6 years, respectively. Phase 1 trials of biologics have a mean treatment period of 12.7 months; Phase 1 trials of small molecules have a mean treatment period of 3.0 months. On average, cognitive enhancer treatment exposure periods in Phase 1 trials are 1.8 months and trials for neuropsychiatric agents have a 1-month treatment period.

3.5 | Biomarkers in trials

In Phase 3 trials, amyloid PET (11 trials) cerebrospinal fluid (CSF) amyloid (9 trials), CSF amyloid/tau ratios (2 trials) are collected at entry. Tau PET (1 trial), CSF p-tau (4 trials), and CSF tau (2 trials) are collected at baseline. Plasma amyloid (3 trials), plasma p-tau (1 trial), and amyloid/tau ratio (1 trial) were collected in other trials. Among DMT trials, 4 trials (all studying small molecules) did not include a biomarker as part of the entry criteria as listed on clinicaltrials.gov.

In Phase 2 trials amyloid PET (30 trials) CSF amyloid (25 trials), CSF amyloid/tau ratios (3 trials) are collected at entry. Tau PET (5 trials), CSF tau (6 trials), and CSF p-tau (6 trials) are collected at baseline. Plasma amyloid (4 trials) and plasma p-tau (1 trial) are collected at baseline in Phase 2 trials. Eleven DMT Phase 2 did not include biomarker collection at baseline as registered on clinicaltrials.gov.

CSF plays a key role in Phase 1 with CSF amyloid collected in four trials, tau in two trials, p-tau in two trials, and amyloid/tau ratios in two trials. Amyloid and tau PET are used in three and one trials, respectively. Plasma p-tau is collected in one as shown on clinicaltrials.gov. Eleven Phase 1 trials including seven DMTs do not describe collecting biomarkers at baseline as shown on clinicaltrials.gov.

Forty-eight trials in the pipeline do not collect biomarkers at baseline. Seventeen of Phase 3, 20 of Phase 2, and 11 of Phase 1 trials do not collect biomarkers at trial entry. Six trials of DMT biologics (11% of DMT biologic trials), 16 (24% of trial of DMT small molecules) trials of DMT small molecules, 6 (35%) trials of cognitive enhancing agents, and 20 (87%) of trials of drugs addressing neuropsychiatric symptoms do not collect biomarkers at the time of trial initiation.

3.6 | Trial participants

Considered together all current trials require 51,398 participants. To populate all current Phase 3 trials, 36,998 participants are required. Of these, 28,671 are needed for DMT trials (18,232 for trials of biological agents; 10,439 for small molecule trials), 1383 are needed for trials of cognitive enhancing agents, and 6944 for trials of drugs to treat neuropsychiatric symptoms. Populating all current Phase 2 trials, requires 13,138 participants. Of these, 11,037 are needed for DMT trials (5,286 for biologic trials; 5,751 for small molecule trials); 1185

TABLE 2 Agents in Phase 2 Alzheimer's disease drug development (clinicaltrials.gov accessed January 1, 2024).

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
50561	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	RAC1 inhibitor (RAC family small GTPase inhibitors) enhance dendritic spine morphogenesis and synaptic plasticity	NCT05811442	Beijing Joekai Biotechnology LLC	Apr 2023	May 2024
ABBV-552	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	Synaptic vesicle glycoprotein 2A (SV2A) modulator	NCT05771428	AbbVie	Apr 2023	Jun 2024
ABBV-916	Disease-modifying biologic	Amyloid beta	Anti-amyloid antibody	NCT05291234	AbbVie	Aug 2022	Jan 2030
ACI-24.060	Disease-modifying biologic	Amyloid beta	Vaccine stimulates antibodies against amyloid beta protein	NCT05462106	AC Immune SA	Jun 2022	Jun 2026
AL002	Disease-modifying biologic	Inflammation	Monoclonal antibody targeting TREM2 receptors	NCT04592874 NCT05744401	Alector Inc.	Jan 2021 Jan 2023	Sep 2024 Sep 2025
Allopregnanolone	Disease-modifying small molecule	Neurogenesis	Allosteric modulator of GABA-A Receptors	NCT04838301	University of Arizona	Aug 2023	Apr 2025
ALZN002	Disease-modifying biologic	Amyloid beta	Autologous Beta-Amyloid Mutant Peptide-pulsed Dendritic Cells	NCT05834296	Alzamend Neuro, Inc.	Jul 2023	Mar 2028
APH-1105	Disease-modifying small molecule	Amyloid beta	Alpha-secretase modulator (amyloid precursor protein secretase modulator)	NCT03806478	Aphios	Jun 2023	Sep 2024
Astragalus	Cognitive enhancement	Inflammation	Undisclosed	NCT05647473	Fujian Medical University Union Hospital	Feb 2024	May 2025
Bacillus Calmette-Guerin	Disease-modifying biologic	Inflammation	Vaccine to stimulate resilience to Alzheimer-related processes	NCT05004688	Steven E Arnold, MD	Mar 2022	Oct 2023
Baricitinib	Disease-modifying small molecule	Inflammation	Janus kinase (JAK) inhibitor	NCT05189106	Massachusetts General Hospital	Dec 2022	Jul 2024
Bepranemab	Disease-modifying biologic	Tau	Anti-tau monoclonal antibody binding to central region of tau	NCT04867616	UCB Biopharma SRL	Jun 2021	May 2024
BIIB080	Disease-modifying biologic	Tau	Antisense oligonucleotide that inhibits translation of tau mRNA into the tau protein	NCT05399888	Biogen	Aug 2022	Nov 2027
Brivaracetam	Cognitive enhancement	Neurotransmitter receptors	Anticonvulsant with high affinity for synaptic vesicle protein 2A	NCT05899764	University of California, Los Angeles	Jun 2023	Jun 2028
Bumetanide	Disease-modifying small molecule	ApoE, lipids and lipoprotein receptors	Reversal of ApoE-specific AD signatures	NCT06052163	Stanford University	Oct 2023	Oct 2025
Canakinumab	Disease-modifying biologic	Inflammation	Anti-IL-1-beta monoclonal antibody	NCT04795466	Novartis Pharmaceuticals	Oct 2021	Mar 2024

(Continues)

TABLE 2 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
Cannabidiol	Neuropsychiatric symptom	Neurotransmitter receptors	Endocannabinoid receptor agonist	NCT05822362	University of Colorado, Denver	Jan 2024	Apr 2028
Chinese Traditional Medicine	Cognitive enhancement	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	Cognitive enhancement	Growth factors and hormones	Selective glucocorticoid receptor antagonist	NCT04601038	Johns Hopkins University	Jun 2021	Jun 2025
CST-2032	Cognitive enhancement	Neurotransmitter receptors	Noradrenergic agonist	NCT05104463	CuraSen Therapeutics, Inc.	Apr 2022	Nov 2023
CT1812	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	Sigma 2 receptor antagonist; binds to sigma-2/PGRMC1 receptor and regulates Aβ oligomer-mediated synaptic toxicity	NCT03507790 NCT05531656	Cognition Therapeutics	Oct 2018 Jun 2023	Jul 2024 Apr 2027
Dalzanemdor	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	Enhnaces synaptic function through NMDA receptor blockade	NCT05619692	Sage Therapeutics	Dec 2022	Dec 2024
Dasatinib + Quercetin	Disease-modifying small molecule	Inflammation	Dasatinib induces apoptosis in senescent cells to allow their removal; quercetin is a flavonoid	NCT04685590 NCT04785300 NCT05422885	Wake Forest University Health Sciences James L. Kirkland, MD, PhD Lewis Lipsitz	Dec 2021 Jul 2022 May 2022	Jan 2025 Dec 2023 Jun 2024
Dexmedetomidine	Neuropsychiatric symptom	Neurotransmitter receptors	Presynaptic alpha-2 adrenoceptor agonist to inhibit release of norepinephrine	NCT06052254	Teikoku Pharma USA, Inc.	Dec 2023	Dec 2024
DHA	Disease-modifying small molecule	Oxidative stress	Omega 3 fatty acid; reduce amyloid production; improve synaptic function; antioxidant	NCT03613844	University of Southern California	Sep 2018	May 2024
Dronabinol	Neuropsychiatric symptom	Neurotransmitter receptors	CB1 and CB2 endocannabinoid receptor partial agonist	NCT02792257	Johns Hopkins University	Mar 2017	May 2024
Dronabinol + PEA	Neuropsychiatric symptom	Neurotransmitter receptors	Cannibinoid	NCT05239390	The Israeli Medical Center for Alzheimer's	Dec 2021	Jun 2023
E2814	Disease-modifying biologic	Tau	Anti-tau monoclonal antibody	NCT04971733	Eisai Inc.	Jun 2021	Jul 2025
Edaravone	Disease-modifying small molecule	Oxidative stress	Pyrazolone free-radical scavenger	NCT05323812	Treeway B.V.	Mar 2023	Jan 2024
EX039	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	Inhibits D-amino acids oxidate to increase N-methyl-D-aspartate receptor activity	NCT05413655	Excelsior	Aug 2022	Aug 2025
ExPlas	Disease-modifying biologic	Synaptic plasticity/neuroprotection	Plasma transfusion from exercise-trained donors	NCT05068830	Norwegian University of Science and Technology	Sep 2021	Sep 2024

(Continues)

TABLE 2 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
Flos gossypii flavonoids	Disease-modifying small molecule	Oxidative stress	Antioxidant; anti-inflammatory	NCT05269173	Capital Medical University	Oct 2020	Jun 2024
GSK4527226	Disease-modifying biologic	Proteostasis/ proteinopathies	Monoclonal antibody to sortilin (SORT1) to improve lysosomal function	NCT06079190	GlaxoSmithKline	Oct 2023	Dec 2026
Hydroxypropyl beta-cyclodextrin	Disease-modifying 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	Neuropsychiatric symptom	Neurotransmitter receptors	Cannabinoid	NCT05543681	IGC Pharma LLC	Oct 2022	Jun 2025
Insulin	Disease-modifying biologic	Metabolism and bioenergetics	Decreases glucose resistance; increase insulin signaling in the brain	NCT05006599	Wake Forest University Health Sciences	May 2025	May 2029
Insulin + Empagliflozin	Disease-modifying 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
Interleukin-2	Disease-modifying biologic	Inflammation	Restore function of regulatory T cells	NCT06096090	The Methodist Hospital Research Institute	Mar 2023	Dec 2025
IVL3003	Cognitive enhancement	Neurotransmitter receptors	Cholinesterase inhibitor	NCT05345509	Inventage Lab., Inc.	Apr 2023	Mar 2024
JNJ-63733657	Disease-modifying biologic	Tau	Monoclonal antibody targeted at soluble tau (mid-region of tau)	NCT04619420	Janssen Research & Development, LLC	Jan 2021	Mar 2025
JZP541	Neuropsychiatric symptom	Neurotransmitter receptors	Cannabinoid receptor agonists of the endocannabinoid system	NCT06014424	Sunnybrook Health Sciences Center	Sep 2023	Dec 2026
Lamivudine	Disease-modifying small molecule	Epigenetic regulators	Human immunodeficiency virus nucleoside analog reverse transcriptase inhibitor	NCT04552795	Bess Frost, PhD	Feb 2021	May 2023
Lecanemab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody directed at amyloid protofibrils and amyloid plaques	NCT01767311	Eisai Inc.	Dec 2012	Feb 2025
Lenalidomide	Disease-modifying small molecule	Inflammation	Anti-inflammatory and immunomodulatory originally approved to treat multiple myeloma	NCT04032626 NCT06177028	St. Joseph's Hospital and Medical Center, Phoenix	Jul 2020 Jan 2024	Sep 2023 Jan 2026
Leuprorelin	Disease-modifying small molecule	Growth factors and hormones	Gonadotropin releasing hormone (GnRH) receptor agonist	NCT03649724	Weill Medical College of Cornell University	Nov 2020	Feb 2025
Levetiracetam	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	SV2A modulator enhancing synaptic plasticity	NCT03875638 NCT04004702	Beth Israel Deaconess Medical Center Walter Reed National Military Medical Center	Aug 2019 Jan 2020	Aug 2023 Dec 2024

(Continues)

TABLE 2 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
L-Serine	Disease-modifying small molecule	Inflammation	Naturally-occurring dietary amino acid; inhibits toxic misfolding	NCT03062449	Aleksandra Stark	Mar 2017	Dec 2022
LX1001	Disease-modifying biologic	ApoE, lipids and lipoprotein receptors	Adeno-associated virus (AAV) gene transfer vector expressing the cDNA coding for human apolipoprotein E2 (APOE2) directly to the CNS/CSF of APOE4 homozygotes	NCT03634007	Lexeo Therapeutics	Nov 2019	Nov 2024
LY3372689	Disease-modifying small molecule	Tau	O-GlcNAcase enzyme inhibitor	NCT05063539	Eli Lilly and Company	Sep 2021	Jul 2024
Memantine	Disease-modifying small molecule	Neurotransmitter receptors	NMDA receptor antagonist	NCT05063851	University of Virginia	Oct 2021	Dec 2025
Methylene Blue	Disease-modifying small molecule	Tau	Tau protein aggregation inhibitor	NCT02380573	The University of Texas Health Science Center at San Antonio	Jul 2015	Apr 2022
MIB-626	Disease-modifying small molecule	Amyloid beta	Sirtuin-nicotinamide adenine dinucleotide stimulator to enhance alpha-secretase	NCT05040321	Brigham and Women's Hospital	Dec 2021	Apr 2024
Montelukast buccal film	Disease-modifying small molecule	Inflammation	Leukotriene receptor antagonist (LTRA); anti-inflammatory effects	NCT03402503	IntelGenx Corp.	Nov 2018	Feb 2024
MW150	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	p38 alpha MAPK kinase inhibitor	NCT05194163	Neurokine Therapeutics	May 2022	Aug 2024
NanoLithium NP03	Disease-modifying small molecule	Neurotransmitter receptors	Ion with effects on amyloid, oxidation, and inflammation	NCT05423522	Medesis Pharma SA	May 2022	Jan 2024
Nicotine transdermal patch	Cognitive enhancement	Neurotransmitter receptors	Nicotinic acetylcholine receptor agonist	NCT02720445	University of Southern California	Jan 2017	Aug 2025
Pegipanermin	Disease-modifying biologic	Inflammation	Neutralizes TNF-alpha	NCT05318976 NCT05522387	Inmune Bio, Inc.	Feb 2022 Feb 2023	Dec 2024 May 2026
Pepinemab	Disease-modifying biologic	Inflammation	Monoclonal antibody directed at semaphorin 4D; reduces inflammatory cytokine release	NCT04381468	Vaccinex Inc.	Jul 2021	Jun 2023
PRI-002	Disease-modifying small molecule	Amyloid beta	Interferes with oligomerization of A-beta 42 to prevent formation and enhance reduction of A-beta oligomers	NCT06182085	PRInnovation GmbH	Dec 2023	Apr 2026

(Continues)

TABLE 2 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
PrimeC	Disease-modifying small molecule	Inflammation	Combined product targeting inflammation, iron accumulation, impaired RNA regulation	NCT06185543	NeuroSense Therapeutics Ltd.	Nov 2023	Nov 2025
Proleukin	Disease-modifying biologic	Inflammation	IL-2 immunomodulator	NCT05468073	Center Hospitalier St Anne	Oct 2022	Sep 2025
Rapamycin	Disease-modifying small molecule	Proteostasis/ proteinopathies	Autophagy enhancer; MTOR inhibitor; immunomodulator	NCT04629495 NCT06022068	The University of Texas Health Science Center at San Antonio Karolinska Institutet	Aug 2021 Sep 2023	Dec 2023 Jan 2025
REM0046127	Cognitive enhancement	Neurotransmitter receptors	Modulates Orai calcium (Ca2+) channel activity to normalize neuronal Ca2+ homeostasis	NCT05478031	reMYND	Jun 2022	Jun 2023
Sargramostim	Disease-modifying biologic	Inflammation	Hematopoietic growth factor granulocyte macrophage colony stimulating factor; anti-inflammatory	NCT04902703	University of Colorado, Denver	Jun 2022	Jul 2024
Seltorexant	Neuropsychiatric symptom	Circadian rhythm	Dual orexin receptor antagonist	NCT05307692	Janssen Research & Development, LLC	May 2022	Oct 2023
Senicapoc	Disease-modifying small molecule	Inflammation	Calcium-activated potassium channel inhibitor	NCT04804241	University of California, Davis	Mar 2022	Dec 2024
Simufilam	Disease-modifying small molecule	Synaptic plasticity/neuroprotection	Filamin A conformation stabilizer; disrupts the interaction of filamin A with the alpha 7 nicotinic acetylcholine receptor to reduce tau hyperphosphorylation and neurodegeneration; dependent on A-beta's signaling via the alpha 7 pathway	NCT05352763	Cassava Sciences, Inc.	May 2022	Oct 2025
Suvorexant	Disease-modifying small molecule	Neurotransmitter receptors	Dual orexin receptor antagonist	NCT04629547	Washington University School of Medicine	May 2022	May 2026
TB006	Disease-modifying biologic	Inflammation	Monoclonal antibody targeting galactose-specific lectin (galectin) 3, a β-galactosidase-binding protein that activates macrophages; anti-inflammatory	NCT05476783	TrueBinding, Inc.	Sep 2022	Oct 2024
Tdap	Disease-modifying 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	Lead sponsor	Start date	Estimated primary completion date
Telmisartan	Disease-modifying small molecule	Vasculature	Angiotensin II receptor blocker	NCT02085265	Sunnybrook Health Sciences Center	Mar 2014	Sep 2023
Tertomotide	Disease-modifying biologic	Synaptic plasticity/neuroprotection	Human telomerase reverse transcriptase (hTERT) mimic	NCT05189210	GemVax & Kael	Oct 2022	Jul 2023
THC-free cannabidiol	Neuropsychiatric symptom	Neurotransmitter receptors	Cannabinoid	NCT04436081	Eastern Virginia Medical School	Feb 2021	Mar 2024
Trazodone	Cognitive enhancement	Circadian rhythm	Serotonin reuptake inhibitor	NCT05282550	Johns Hopkins University	Jan 2023	Mar 2027
Trontinemab	Disease-modifying biologic	Amyloid beta	Monoclonal antibody directed at plaques and oligomers; "brain-shuttle" gantenerumab	NCT04639050	Hoffmann-La Roche	Mar 2021	Sep 2027
Valacyclovir	Disease-modifying small molecule	Inflammation	Anti-viral against HSV-1 and –2; reduces vira-related 'seeding' of amyloid plaque deposition	NCT03282916	Columbia University	Feb 2018	Dec 2024
Valiltramiprosate	Disease-modifying small molecule	Amyloid beta	Aggregation Inhibitor	NCT04693520	Alzheon Inc.	Sep 2020	Jul 2023
Varoglutamstat	Disease-modifying small molecule	Amyloid beta	Glutaminyl cyclase (QC) enzyme inhibitor to reduce production of pyroglutamate Aβ	NCT03919162 NCT04498650	Vivoryon Therapeutics N.V.	Nov 2021 Jul 2020	Nov 2023 Jan 2024
Wei Li Bai	Disease-modifying small molecule	Metabolism and bioenergetics	Not specified; reported to regulate metabolism, improve blood circulation, and exert anti-inflammatory and antioxidant effects	NCT05670912	Capital Medical University	Oct 2022	Nov 2024
Xanamem	Cognitive enhancement	Growth factors and hormones	11-beta-hydroxysteroid dehydrogenase type 1 inhibitor	NCT06125951	Actinogen Medical	Dec 2023	Dec 2025
Yangxue Qingnao pills	Disease-modifying small molecule	Vasculature	Cerebral blood flow enhancer; traditional Chinese herbal medicine	NCT04780399	Dongzhimen Hospital, Beijing	Nov 2021	Mar 2024

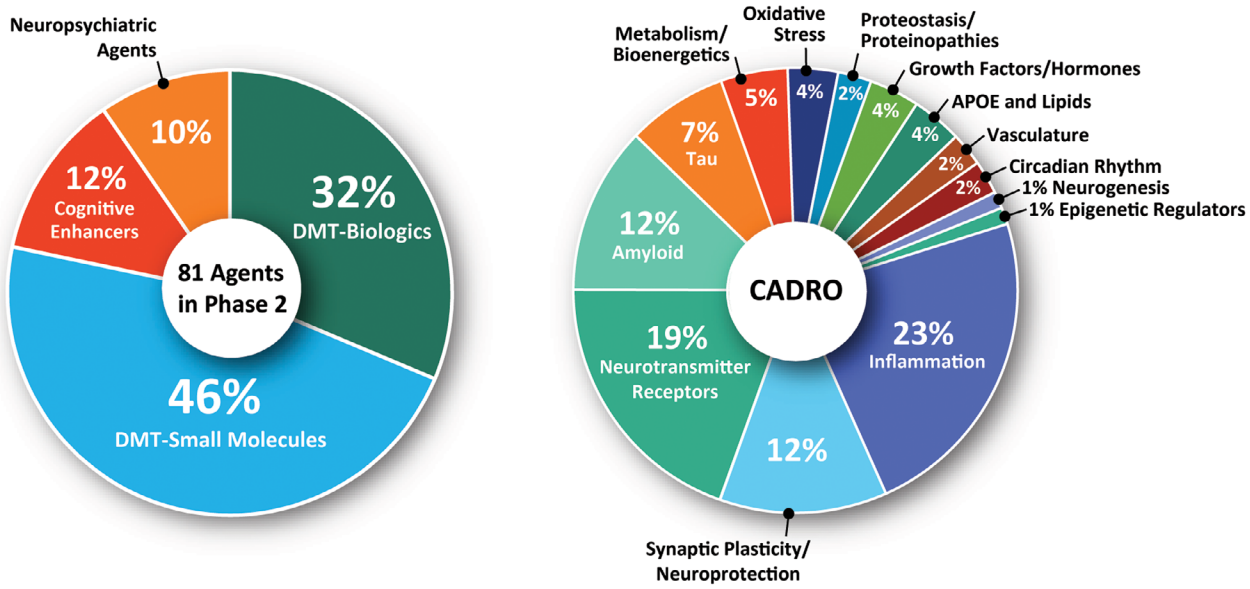

FIGURE 4 Mechanisms of action of agents in Phase 2 Alzheimer clinical trials as classified using 4 categories of therapeutic purpose (left) or the Common Alzheimer's Disease Research Ontology (CADRO) approach (right)(figure © J Cummings; M de la Flor, PhD, Illustrator).

are needed for trials of cognitive enhancing agents; and 916 for trials of drugs to treat neuropsychiatric symptoms. Current Phase 1 trials require 1,262 participants. Of these, 1,054 are needed for DMT trials (705 for biologic trials; 349 for small molecule trials), 176 are needed for trials of cognitive enhancing agents, and 32 for trials of drugs to treat neuropsychiatric symptoms.

3.7 | Global trial distribution

Of the 45 trials in Phase 3 whose location is recorded, 56% (25 trials) are global with both North American and non-North American sites. Twenty-nine percent (13 trials) are performed in North America only and 16% (7 trials) are being performed only in non-North American sites. Of the 85 trials in Phase 2 whose location is recorded, 25% (21 trials) are global with both North American and non-North American site. Fifty-one percent (43 trials) are performed in North America only, and 25% percent (21 trials) are being performed only in non-North American sites. Of the 25 trials in which the Phase 1 trial location is included in the registration, 64% ($N = 16$) are conducted in North America only; 7 (28%) include only non-North American sites; and 2 (8%) include both North American and non-North American sites. In total, of the trials with location recorded, 31% are conducted globally with both North American and non-North American sites; 46% are conducted in North America only; and 23% are conducted outside of North America with no North American sites participating.

3.8 | Repurposed agents

The 39 repurposed agents comprise 31% of drugs in the AD drug development pipeline. They comprise nine agents in Phase 3; 28 agents of Phase 2, and seven agents of Phase 1. Six agents (15%) of repurposed agents are DMT biologics, 21 (54%) are DMT small molecules, 6 (15%) are cognitive enhancers, and 6 (15%) are drugs for NPS. The 21 repurposed DMT small molecules represent 40% of DMT small molecules in the AD pipeline.

The number of new chemical entities (NCEs) in the AD drug development pipeline declined disproportionately. There were 101 NCEs in the 2023 pipeline and there are 88 NCEs in the 2024 pipeline, representing a 13% drop.

3.9 | Trial funders

Sixty percent of clinical trials are industry funded including 79% of Phase 3 trials, 51% of Phase 2 trials, and 54% of Phase 1 trials.

The funding pattern for trials with repurposed agents differs from that of most trials in the pipeline. Seventy-seven percent of repurposed trials are funded by non-industry sources. Fifty-eight percent of Phase 3 trials, 82% of Phase 2 trials, and 86% of Phase 1 trials are funded through non-industry sources.

For NCEs, 77% are industry funded including 92% of Phase 3 NCE trials, 70% of Phase 2 NCE trials, and 68% of Phase 1 NCE trials.

3.10 | Combination therapies

Combination therapies are present in the 2024 AD drug development pipeline. One pharmacodynamic combination is Tdap, a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine associated with a reduction in the occurrence of AD in epidemiologic studies.[12] The Dominantly Inherited Alzheimer's Disease—Treatment Unit (DIAN-TU) will include assessment of the

TABLE 3 Agents in Phase 1 Alzheimer's disease drug development (clinicaltrials.gov accessed January 1, 2024).

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
Allopregnanolone	Disease-modifying small molecule	Neurogenesis	Allosteric modulator of GABA-A Receptors	NCT03748303	University of Arizona	Oct 2019	Dec 2022
ALN-APP	Disease-modifying biologic	Amyloid beta	RNAi to decrease APP and downstream Aβ-related events	NCT05231785	Alnylam Pharmaceuticals	Feb 2022	Jul 2025
ALZ-101	Disease-modifying biologic	Amyloid beta	Amyloid beta-directed vaccine	NCT05328115	Alzinova AB	Sep 2021	Dec 2023
APNmAb005	Disease-modifying biologic	Tau	Anti-tau antibody	NCT05344989	APRINOIA Therapeutics, LLC	May 2022	Mar 2024
AV-1959	Disease-modifying biologic	Amyloid beta	Anti-amyloid vaccine	NCT05642429	Institute for Molecular Medicine	Feb 2023	Feb 2026
Bacillus Calmette-Guerin	Disease-modifying biologic	Inflammation	Vaccine to stimulate resilience to Alzheimer-related processes	NCT06078891	Tamir Ben-Hur	Jul 2023	Jul 2024
BMS-984923	Disease-modifying small molecule	Amyloid beta	Silent allosteric modulator (SAM) of mGluR5	NCT05804383 NCT05817643	Allyx Therapeutics	Mar 2023 Jan 2023	Oct 2024 Feb 2023
Cannabidiol	Neuropsychiatric symptom	Neurotransmitter Receptors	Cannabinoid	NCT04075435	Mclean Hospital	Jan 2021	Sep 2024
Centella asiatica product	Disease-modifying small molecule	Synaptic Plasticity/Neuroprotection	Antioxidant and anti-inflammatory agent with synaptic and neuroprotective effects	NCT05591027	Oregon Health and Science University	Dec 2022	Nov 2024
Choline	Disease-modifying small molecule	Metabolism and Bioenergetics	Stabilizes the lipid metabolism and concomitantly restoring normal cell function by increasing phosphatidylcholine activity via the Kennedy pathway	NCT05880849	Paul E Schulz	Jun 2023	Jun 2025
CpG1018	Disease-modifying biologic	Inflammation	Toll-like receptor nine agonist leading to reduced Aβ plaques and tau pathology	NCT05606341	NYU Langone Health	Mar 2023	Nov 2024
CS6253	Disease-modifying biologic	ApoE, Lipids and Lipoprotein Receptors	Adenosine triphosphate-binding cassette transporter A1 (ABCA1) transfers lipids to ApoE, and increases clearance of A-beta from the brain	NCT05965414	Artery Therapeutics, Inc.	Oct 2023	Sep 2024
Donepezil	Cognitive enhancement	Neurotransmitter Receptors	Cholinesterase inhibitor	NCT06127368	G2GBio, Inc.	Jan 2024	Sep 2024
Emtricitabine	Disease-modifying small molecule	Inflammation	Nucleoside reverse transcriptase inhibitor (NRTI)	NCT04500847	Butler Hospital	Dec 2021	Mar 2024

(Continues)

TABLE 3 (Continued)

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
IBC-Ab002	Disease-modifying biologic	Inflammation	Anti-programmed death-ligand 1 (PD-L1) immune checkpoint inhibitor	NCT05551741	Immunobrain Checkpoint	Feb 2023	Oct 2024
LX1001	Disease-modifying biologic	ApoE, Lipids and Lipoprotein Receptors	Adeno-associated virus (AAV) gene transfer vector expressing the cDNA coding for human apolipoprotein E2 (APOE2) directly to the CNS/CSF of APOE4 homozygotes	NCT05400330	Lexeo Therapeutics	May 2023	Nov 2028
Mecamylamine	Cognitive enhancement	Neurotransmitter Receptors	Nicotinic antagonist	NCT04129060	University of Vermont	Mar 2020	Mar 2024
MK-2214	Disease-modifying biologic	Tau	Anti-tau monoclonal antibody	NCT05466422	Merck Sharp & Dohme LLC	Sep 2022	May 2025
Nicotinamide Riboside	Disease-modifying small molecule	Metabolism and Bioenergetics	Mitochondrial function enhancer and antioxidant	NCT04430517	Mclean Hospital	Mar 2022	Apr 2025
NIO752	Disease-modifying biologic	Tau	Anti-tau antisense oligonucleotide	NCT05469360	Novartis Pharmaceuticals	Feb 2023	Oct 2024
OLX-07010	Disease-modifying small molecule	Tau	Inhibits tau self-aggregation	NCT05696483	Oligomerix, Inc	Jan 2023	Dec 2024
Probiotic Blend Capsule	Disease-modifying small molecule	Gut-Brain Axis	Inflammation/immunity	NCT06181513	University of Nicosia	Dec 2022	Jul 2024
Psilocybin	Neuropsychiatric symptom	Neurotransmitter Receptors	Psychedelic	NCT04123314	Johns Hopkins University	Mar 2021	Dec 2024
Remternetug	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody	NCT04451408	Eli Lilly and Company	Jul 2020	Aug 2024
SHR-1707	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody	NCT06114745	Atridia Pty Ltd.	Jan 2024	Nov 2025

TABLE 4 Minimal, mean, and maximal study durations (treatment plus recruitment) for Phase 1, Phase 2, and Phase 3 trials of DMT biologics, DMT small molecules, cognitive enhancing agents, and drugs for neuropsychiatric syndromes (prevention trials not included).

Therapeutic purpose	Relative duration	Phase 1	Phase 2	Phase 3	Total; weeks	Total; years
DMT; biologic	Minimal	49.0	47.9	104.3	201.2	3.9
	Mean	141.9	218.9	302.3	663.1	12.7
	Maximal	286.3	635.0	773.9	1695.2	32.5
DMT; small molecule	Minimal	74.6	58.6	43.7	176.9	3.4
	Mean	124.7	184.5	195.8	505.0	9.7
	Maximal	191.3	495.9	291.7	978.9	18.8
Cognitive enhancing agent	Minimal	53.9	52.1	156.6	262.6	5
	Mean	136.8	178.9	206.7	522.4	10
	Maximal	219.7	446.0	243.7	909.4	17.4
Drugs for NPS	Minimal	191.9	52.3	79.0	323.2	6.2
	Mean	194.3	165.6	219.5	579.4	11.1
	Maximal	196.7	378.3	500.0	1075.0	20.6

Abbreviations: DMT, Disease-modifying therapy; NPS, neuropsychiatric symptoms.

combination of lecanemab, an anti-amyloid agent, and E2814 and anti-tau agent. Several trials are assessing the combination of dasatinib and quercetin for its senolytic activity in AD, and a combination of insulin and empagliflozin addresses metabolic and bioenergetic pathways. A combination of dronabinol (tetrahydrocannabinol) and palmitoylethanolamide (an endogenous cannabinoid with putative anti-inflammatory properties) is being used in a trial to treat agitation in AD.

Pharmacokinetic combinations are also evident in the pipeline. AVP-786 is a putative anti-agitation agent consisting of dextromethorphan and quinidine[13]; AXS-05 is being assessed as an anti-agitation agent consisting of dextromethorphan and bupropion[14]; and KarXT, consisting of a combination of this xanomeline and trospium, is an being tested as an antipsychotic agent.

Other types of combinations include trontinemab, a combination of gantenerumab and a transferrin-based brain-shuttle,[15] and a combination of aducanumab with focused ultrasound to increase the entry of aducanumab into the brain through the blood-brain barrier.[16]

3.11 | Total study duration and implications for drug development time requirements

Examination of the duration of each phase of drug development provides insight into the average time required to advance a drug through the pipeline. The study time on clinicaltrials.gov is comprised of the total of the recruitment time plus the treatment exposure time. The number represents the period from the initiation of the study to primary completion date of the study. As shown in Table 4, the mean durations of the three phases of drug development for a DMT biologic sum to 12.7 years, for a DMT small molecule 9.7 years, for a cognitive enhancing agent 10 years, and for a drug for neuropsychiatric symptoms 11.1 years.

4 | DISCUSSION

In 2023, the FDA approved - 55 NCEs and 18 biologics—across all therapeutic areas. One drug—the anti-amyloid MAB, lecanemab—was approved for AD.[7] Another agent, brexpiprazole, was approved by the FDA for the treatment of agitation associated with dementia due to AD. It is not a novel agent since it is approved for other indications; it is the first drug approved for agitation or any neuropsychiatric syndrome associated with AD. There were approvals of treatments for two other neurodegenerative diseases including toferson—an antisense oligonucleotide (ASO)—to treat amyotrophic lateral sclerosis in adults who have a superoxide dismutase 1 (SOD1) gene mutation and omaveloxolone to treat Friedreich's ataxia. This trend suggests that new means of intervening in neurodegenerative disorders are being discovered.

The 164 trials and 127 drugs in the current AD drug development pipeline compares to 187 trials assessing 141 drugs for AD in 2023. There is a disproportionate decrease in the number of NCEs in the pipeline (e.g., from 101 to 88, representing a 13% decrease). NCEs are more likely to be sponsored by industry and more likely to be advanced to Phase 3 if early phase trials are promising. Repurposed agents are disproportionately funded through non-industry sources and are less likely to advance to Phase 3.

Currently, there are 24 agents targeting neuroinflammation in the pipeline, comprising 19% of all therapeutic agents in the pipeline. The canonical targets of amyloid, tau, and neurodegeneration (ATN),[17] have 20 (16% of the pipeline agents), 10 (8%), and 0 active agents, respectively, in the pipeline representing 24% of agents. Within each of the CADRO categories, nearly every agent being studied has a different MoA and a different approach to modulating the target process.

Recruitment of a sufficient number of trial participants is a major issue for conduct of clinical trials in a timely way. On average, it takes 2.1 years to recruit the populations for a Phase 1 trial, 2.5

years to recruit enough subjects for a Phase 2 trial, and 3.2 years for recruitment of subjects for a Phase 3 trial. These recruitment time frames are largely applicable across therapeutic areas. Although many fewer patients are required for clinical trials assessing agents for the treatment of neuropsychiatric syndromes, enrolling participants with AD and exhibiting specific behavioral features is more challenging than recruiting participants with AD and no required neuropsychiatric symptoms. The approval of lecanemab and the possible approval of donanemab may affect recruitment if patients choose approved over experimental therapies. Identifying strategies to increase interest in trial participation and improve trial recruitment could have a major impact on accelerating drug development for AD.

Study of the mean, minimal, and maximal duration of trials for each of the phases for drugs of different therapeutic classes provides insight into the total duration of drug development programs for AD. DMT small molecules are the most common agent in the AD pipeline. On average, these drugs require 9.7 years to complete one trial in each of the three development phases. There is typically 1 year between phases for data review, next phase planning, and regulatory interactions. This would add 2 years to the total development time. In addition, most trials require at least 1 year of nonclinical studies prior to first-in-human exposures. An agent that goes for regulatory review following a Phase 3 trial will add 12–18 months to the total program time. Beginning with 9.7 years as the mean time for one trial in each phase; adding 2 years for between trial decisions and 1 year for nonclinical testing would result in an average development time of 13 years. A total of 6-12 months of additional time would be required if the Phase 3 results are positive and FDA review of possible approval is required (total 13.5-14 years). This observation is similar to the conclusion reached by Scott and colleagues in a 2014 study of the AD drug development pipeline.[18] This might suggest that the increased technological complexity involved in current AD trials is not increasing the drug development duration and that greater experience in clinical trial conduct is not decreasing the time required for AD drug development.

Combination therapies including pharmacodynamic combinations, pharmacokinetic combinations and combinations aimed at enhancing penetration of the blood brain barrier are evident in the 2024 AD drug development pipeline. Combinations of experimental agents with approved anti-amyloid monoclonal antibodies are anticipated as patients being treated with these agents participate in clinical trials of emerging therapeutics.

AD therapeutics have made remarkable progress. The approval of aducanumab in 2021 ended a 17 year period during which no new AD therapeutics were approved.[5] The accelerated approval of lecanemab followed by its standard approval in 2023 was based on growing evidence that reduction of amyloid plaque as demonstrated by amyloid PET was associated with slowing of cognitive decline.[7] Donanemab is currently under review by the FDA and interrogation of the trial data will provide more insight into the relationship between slowing of cognitive decline and findings on amyloid and tau PET.[6] The atypical antipsychotic, brexpiprazole, was approved in 2023 for the treatment of agitation in dementia associated with AD, becoming the first approved therapy for any neuropsychiatric syndrome in AD.[8] Data are emerging that may allow plasma biomarkers to replace amyloid PET and CSF studies of AD markers for diagnosis.[19] This will facilitate patient recruitment and improve trial quality by confirming the presence of the target disease. Learnings about appropriate biological targets, effective pharmacology, biomarkers to guide diagnosis and clinical trials, and new trial designs and analysis are positioned to accelerate drug development for AD. Continued investment from governmental sources, advocacy groups, philanthropies, and biotechnology and pharmaceutical companies is critical to capitalize on this growing knowledge base and advance therapeutics for patients requiring new therapies.

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CONFLICT OF INTEREST STATEMENT

J.C. has provided consultation to Acadia, Actinogen, Acumen, AlphaCognition, ALZpath, Aprinoia, AriBio, Artery, Biogen, Biohaven, BioVie, BioXcel, Bristol-Myers Squib, Cassava, Cerecin, Diadem, Eisai, GAP Foundation, GemVax, Janssen, Jocasta, Karuna, Lighthouse, Lilly, Lundbeck, LSP/eqt, Mangrove Therapeutics, Merck, NervGen, New Amsterdam, Novo Nordisk, Oligomerix, ONO, Optoceutics, Otsuka, Oxford Brain Diagnostics, Prothena, ReMYND, Roche, Sage Therapeutics, Signant Health, Simcere, sinaptica, Suven, TrueBinding, Vaxxinity, and Wren pharmaceutical, assessment, and investment companies. J.C. owns the copyright of the Neuropsychiatric Inventory. J.C. has stocks/options in Artery, Vaxxinity, Behrens, Alzheon, MedAvante-Prophase, Acumen. GL is a full-time employee of Eisia Co, Ltd. KZ is CEO of CNS Innovations. Y.Z. and J.F. declare no competing interests. F.C. declare no other competing interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

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