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REVIEW ARTICLE

Alzheimer's disease drug development pipeline: 2025

Jeffrey L. Cummings[1,2] | **Yadi Zhou**[3] | **Garam Lee**[1,2] | **Kate Zhong**[1,2] | **Jorge Fonseca**[4] | **Amanda M. Leisgang-Osse**[1,2] | **Feixiong Cheng**[3,5,6,7]

[1]Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, Kirk Kerkorian School of Medicine, University of Nevada, Las Vegas (UNLV), Las Vegas, Nevada, USA

[2]Department of Brain Health, Kirk Kerkorian School of Medicine, University of Nevada, Las Vegas (UNLV), Las Vegas, Nevada, USA

[3]Genomic Medicine Institute, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA

[4]Howard R Hughes College of Engineering, Department of Computer Science, University of Nevada, Las Vegas (UNLV), Las Vegas, Nevada, USA

[5]Department of Molecular Medicine, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

[6]Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

[7]Cleveland Clinic Genome Center, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA

Correspondence
Jeffrey Cummings, Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, Kirk Kerkorian School of Medicine, University of Nevada, Las Vegas (UNLV), Las Vegas, Nevada, USA.
Email: jcummings@cnsinnovations.com

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Abstract

Clinical trials for Alzheimer's disease (AD) must be registered on clinicaltrials.gov. The registry presents a variety of types of information related to the planned clinical trial. We assess clinicaltrials.gov to document and compare aspects of drug development across the AD pipeline. Currently, there are 138 drugs being assessed in 182 clinical trials in the AD pipeline. Biological disease-targeted therapies (DTTs) comprise 30% of the pipeline; small molecule DTTs account for 43% of the pipeline; drugs addressing cognitive enhancement account for 14% of the pipeline; and drugs aiming to ameliorate neuropsychiatric symptoms in participants with AD contribute 11% of the pipeline. Biomarkers are among the primary outcomes of 27% of active trials. Repurposed agents represent 33% of the pipeline agents. The pipeline has more trials and more drugs compared to the 2024 pipeline.

KEYWORDS
Alzheimer's disease, amyloid, biomarkers, clinical trials, Common Alzheimer's Disease Research Ontology (CADRO), drug development, inflammation, pharmaceutical companies, Phase 1, Phase 2, Phase 3, repurposed drugs, synaptic function, tau

Highlights

- The 2025 Alzheimer's disease drug development pipeline hosts 182 trials and 138 novel drugs.
- The 2025 Alzheimer's disease drug development pipeline is diverse, with agents that address 15 basic disease processes.

- The 2025 Alzheimer's disease drug development pipeline has more trials and more drugs than the 2024 pipeline.
- Biomarkers play an important role in current trials to determine trial eligibility and as outcomes of trials.
- Repurposed agents comprise approximately one-third of the agents and trials in the 2025 Alzheimer's disease drug development pipeline.

1 | INTRODUCTION

New therapies are urgently needed for Alzheimer's disease (AD), and progress in understanding the pathophysiology, clinical course, genetics, and biomarkers of the disorder provides the foundation for successful AD-directed drug development.[1] Monoclonal antibodies directed to protofibrillar and pyroglutamate forms of amyloid-beta (Aβ) protein, which remove high molecular weight forms of brain Aβ and have favorable impacts on clinical outcomes, have been approved by the US Food and Drug Administration (FDA) and regulatory agencies.[2,3] Biomarkers were key in these development programs. Approval was dependent on biomarkers to establish the presence of the treatment target and to demonstrate its removal by the intervention.[4] Simultaneously, fluid biomarkers, including plasma measures, have been implemented as drug development tools useful in diagnosis, monitoring, and assessment of pharmacodynamic response in clinical trials.[5,6] Advances in clinical trial design and regulatory definitions of AD stages and approvable outcomes have further enhanced the drug development environment for AD therapies.[7,8] This momentum has benefited anti-amyloid therapies; the rich array of targets for drugs in trials suggests that the invigorated scientific and trial framework may assist development of treatments directed at other targets in a wider range of patients.[9]

We describe the AD drug development pipeline as reflected in the federally mandated clinical trial registry, clinicaltrials.gov. We provide a comprehensive overview of agents in Phase 1, 2, and 3 clinical trials. We report the trial characteristics, clinical outcome measures, and biomarkers. We note the number of participants needed for current trials, the global distribution of trial activity, and the sponsorship of trials. Our goal is to provide information useful in decision-making for trial design, conduct, and analysis, and to assist stakeholders in understanding the landscape of evolving AD therapeutics.

2 | METHODS

Our methodological approach builds on previous AD pipeline reports.[10] The data for this review are derived from clinicaltrials.gov, a clinical trial registry maintained by the US National Library of Medicine of the National Institutes of Health (NIH). All clinical trials conducted in the United States must be registered on clinicaltrials.gov. within 21 days of enrolling the first participant in the trial. The registration requirement applies to trials that have at least one site in the United States, are conducted under an FDA Investigational New Drug (IND) review, or involve a drug that is manufactured in the United States or its territories. Many trials conducted outside the US are registered on clinicaltrials.gov, though the sponsors are not legally obliged to do so. The information on which this report is based is comprehensive but not exhaustive regarding therapeutic agents in clinical trials, since some trials are conducted exclusively outside the United States and are not subject to registration requirements.

Data in clinicaltrials.gov are accessed through the Application Programming Interface (API) and transferred to the database of the UNLV Clinical Trial Observatory and the Cleveland Clinic Laboratory of Network Medicine for analysis and interpretation (regularly updated summary data are available on alzpipeline.com). Raw data are retrieved daily from clinicaltrials.gov as they are posted by clinical trial sponsors using the API data framework. The data (in Json format) is parsed according to the API's data structure to extract more than 30 key data fields. Preliminary filtering is done by combining automatic rule-based programming and manual curation by human annotators to identify specific features of AD trials testing pharmacological interventions. Each trial is annotated for the data fields collected and reported here. All extracted and annotated data are stored in a relational database using PostgreSQL for querying and analysis.

The Index Date for this review is January 1, 2025. Numbers, percentages, and other numerical data provided in this report are accurate regarding clinical trials on the Index Date. Trials reaching their completion date prior to the Index Date or initiated and registered after the Index Date are not included. We include all active trials including those 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 participants are not yet being enrolled). Trials labeled as suspended, terminated, completed, withdrawn, or unknown (defined as having no status update within the past 2 years) are captured in the database but are not included in the calculations involving active trials.

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.

Our search terms include AD or terms related to AD (e.g., dementia of the Alzheimer type), prodromal AD, preclinical AD, and mild cognitive impairment (MCI). Our search algorithms allow for misspellings and grammatical errors observed in the registry. We do not include trials whose participants have dementia of any cause. MCI as a manifestation of a non-AD condition, such as MCI of Parkinson's disease, is excluded.

We capture comprehensive data regarding trials available on clinicaltrials.gov including the name of the test agent, trial title, National Clinical Trial (NCT) identifier number, actual start date, projected primary end date, duration of treatment exposure, number of arms of the study, whether a biomarker was required for eligibility or served as a primary or secondary outcome, and whether the agent was repurposed (e.g., approved for another indication). We note if the trial is a long-term extension of an earlier clinical 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 describe where the trials were performed (North America only; non–North America only with no North American sites; global–North American and non–North American sites included in the trial). We capture the total number of unique trial sites in North America and non–North American global regions that were listed as sites for the AD clinical trials active on the Index Date.

We divide the "lead sponsors" into industry and nonindustry. AD trials not funded by industry are funded by the US National Institute on Aging (NIA), other US federal agencies such as the Veterans Administration, non-US governmental agencies, advocacy groups, or philanthropy.

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

We derive the target process of the agent in the trial based on the descriptive categories of the Common Alzheimer's Disease Research Ontology (CADRO).[11] CADRO categories include Aβ; 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 these categories agents can have one or more specific mechanisms of action (MoAs). The MoAs presented in the tables are derived from clinicaltrials.gov, available literature, informational websites such as alzforum.org, or information provided by the trial sponsor (Tables S1–S3).

Based on mechanistic and target information, we classify agents into Therapeutic Purpose categories as disease-targeted therapies (DTTs) or as symptomatic therapies depending on whether the declared therapeutic purpose is change in a specific aspect of the pathophysiology of AD with the intention of slowing clinical decline or if the intent is to improve symptoms present at baseline in the trial (e.g., improve cognition or reduce neuropsychiatric symptoms [NPS]). "DTT" is preferred to "disease-modifying therapy (DMT)," consistent with the convention of naming drugs according to their intention rather than according to an aspirational outcome. The DTT/symptomatic treatment classification can be ambiguous for some therapies; agents may have multiple therapeutic mechanisms, and drugs may have both DTT and symptomatic properties. We identify the principal therapeutic intent of the agent based on trial characteristics. Trials to demonstrate an impact on disease pathophysiology have designs that differ from those designed to show symptomatic effects. Trials for symptomatic agents are smaller, shorter in duration, and have less reliance on biomarkers, whereas demonstrating the biological and clinical disease impact of a DTT typically requires larger numbers of participants, longer exposures, and more reliance on biomarkers. We divide DTTs into biologics (e.g., monoclonal antibodies, vaccines, antisense oligonucleotides [ASOs]) and small molecules (e.g., drugs typically taken orally and less than 500 Daltons in molecular weight). We divide symptomatic agents into those with putative cognition-enhancing properties and those intended to ameliorate NPS. We specify the type of NPS addressed in the trial (e.g., agitation, psychosis, apathy). 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/).

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

3 | RESULTS

3.1 | Overview

We identified 182 clinical trials assessing 138 drugs in the AD pipeline on the index date of January 1, 2025. This included 48 trials assessing 31 drugs in Phase 3; 86 trials assessing 75 drugs in Phase 2; and 48 trials assessing 45 drugs in Phase 1 (Figure 1). Of the 182 trials, 16 are long-term extensions of agents in prior trials.

The AD drug development pipeline is comprised primarily of DTTs. There was a total of 102 DTTs representing 74% of drugs in clinical trials. Twenty agents (14%) of the pipeline are putative cognitive enhancers, and 15 drugs (11%) are drugs targeting NPS in participants with AD. In the pipeline, 60 (59%) of DTTs are small molecules and 42 (41%) are biological therapies. Phase 3 is comprised of 20 (65%) DTTs; Phase 2 has 60(81%) DTTs; Phase 1 has 33 (73%) DTTs. Repurposed agents approved for non-AD indications comprise 33% (46) of current drugs and 37% (68) of current trials.

Most of the CADRO categories of AD pathophysiology are targeted by at least one drug in current clinical trials (Figure 2). Thirty drugs (22%) of all drugs in the pipeline target neurotransmitter receptors; 25 treatments (18%) target Aβ-related pathophysiology; 24 agents (17%) address neuroinflammation/immune processes; 15 agents (11%) target tau-related processes; 9 drugs (6%) address synaptic

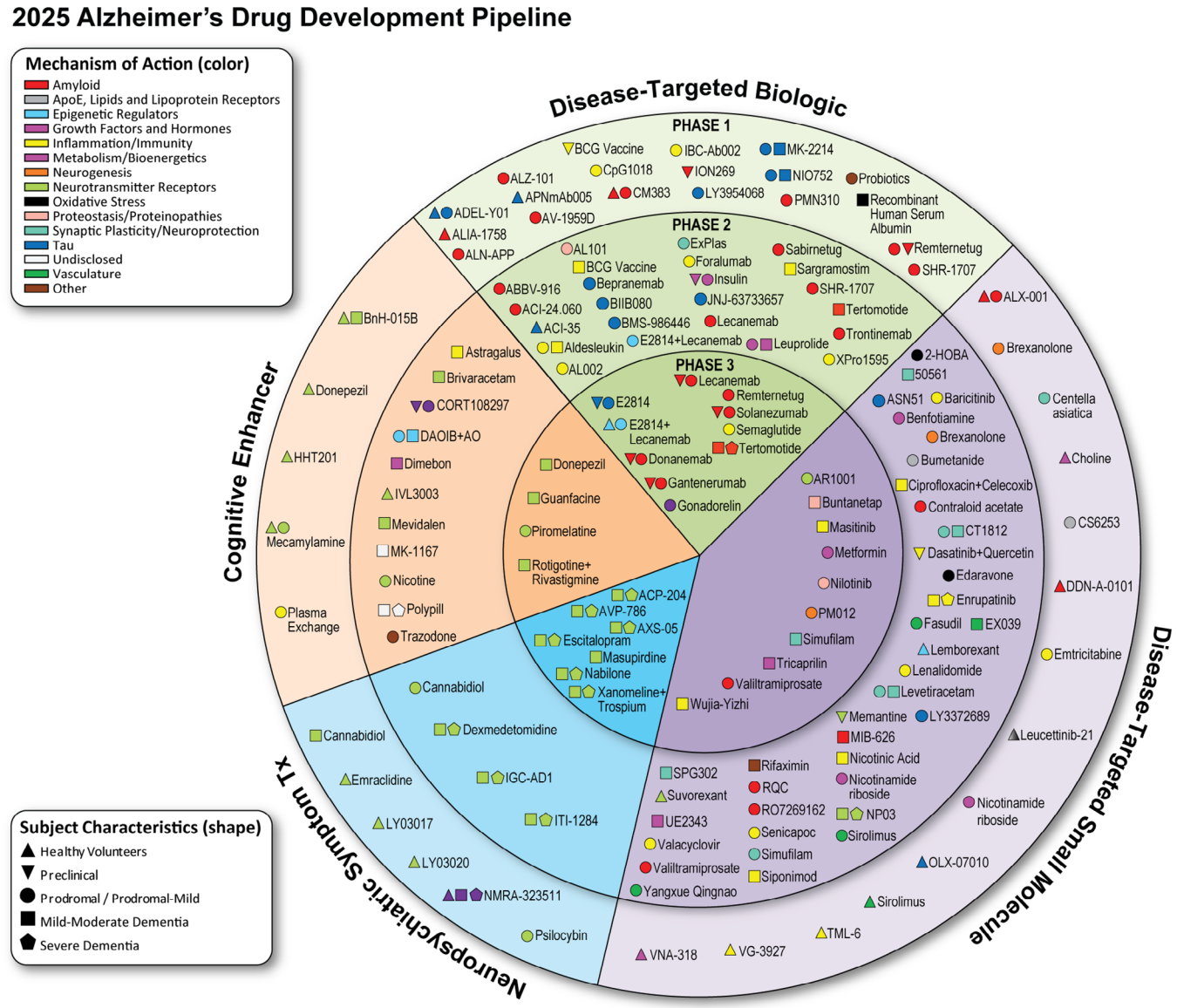

FIGURE 1 Agents in clinical trials for treatment of Alzheimer's disease on the Index Date of January 1, 2025, as recorded on clinicaltrials.gov. The inner ring shows Phase 3 agents; the middle ring includes Phase 2 agents; the outer ring presents Phase 1 therapies. Agents in green areas are biologics; 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 ((C)J. Cummings; M. de la Fleur, PhD, Illustrator). CADRO, Common Alzheimer's Disease Research Ontology.

plasticity/neuroprotection; 8 therapies (6%) target metabolism and bioenergetics; 5 drugs (4%) target growth factors and hormones; 3 drugs (2%) address each of proteostasis/proteinopathy, oxidative stress, and vascular targets; 2 agents (1%) address each of gut–brain axis pathophysiology, neurogenesis, and APOE and lipids/lipoprotein receptors; 1 agent (1%) addresses circadian rhythm disturbances; 3 agents (2%) are described as multi-target; and 3 agents (2%) have undisclosed targets. In total, 15 CADRO categories are included among target processes for drugs in the AD drug development pipeline.

Fifty-six trials in the AD drug development pipeline are new since the last index date (January 1, 2024). There are 10 new trials in Phase 3, 25 new trials in Phase 2, and 21 new trials in Phase 1. Of the drugs that were in the pipeline on the index date of 2024 (January 1, 2024) and are no longer in the pipeline, 25 clinical trials were completed, 8 were terminated, and 8 became of unknown status (no activity registered on clinicaltrials.gov in the past 2 years).

All stages of the AD continuum are represented in current clinical trials. Eight (4%) involving cognitively normal individuals at risk for symptomatic AD; 64 trials (35%) include participants with MCI ascribed to AD or prodromal AD (with or without biomarker confirmation of AD pathology); 48 trials (26%) involve participants with early AD (MCI or mild AD dementia); 103 (57%) allow participants with mild AD dementia, and 75 trials (41%) include participants with moderate or severe AD dementia or AD dementia of any severity (these categories are not mutually exclusive and several trials involve populations from multiple categories).

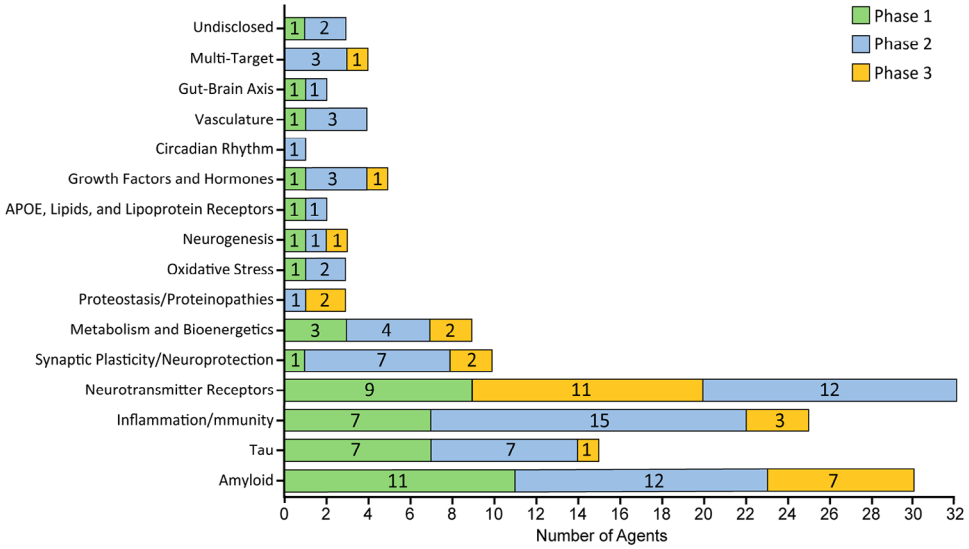

FIGURE 2 Alzheimer-related processes as categorized by the Common Alzheimer's Disease Research Ontology (CADRO) for agents in each phase of the Alzheimer's drug development pipeline (J. Cummings; M. de la Flor, PhD, Illustrator).

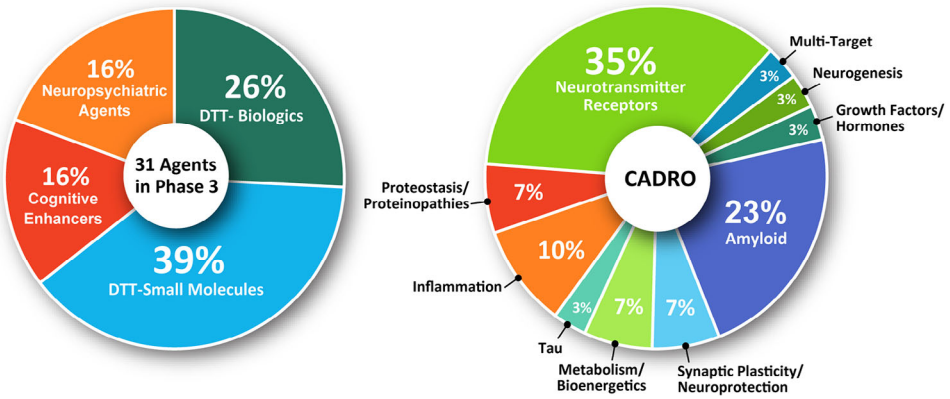

FIGURE 3 Mechanisms of action of agents in Phase 3 Alzheimer clinical trials as classified using four categories of therapeutic purpose (left) or the Common Alzheimer's Disease Research Ontology (CADRO) approach (right) ((C) figure J Cummings; M de la Flor, PhD, Illustrator).

Of all currently active trials with location information, 67 (39%) are conducted only in North America; 47 (28%) are include only areas outside of North America; and 56 (33%) include clinical trial sites both in North America and outside of North America (e.g., are "global").

The biopharmaceutical industry sponsors 112 (62%) of all clinical trials in the current AD pipeline. The biopharmaceutical industry sponsors 36 (75%) of Phase 3 trials, 43 (50%) of Phase 2 trials, and 33 (69%) of Phase 1 trials.

To fully populate currently active trials, 50,109 participants are required: 33,572 in Phase 3, 13,735 in Phase 2, and 2802 in Phase 1.

3.2 | 2 Phase 3 trials

There are 48 Phase 3 trials studying 31 drugs (Table S1; Figure 3). Of the agents in Phase 3, 20 (64%) are DTTs; 5 (16%) target cognitive enhancement; and 6 (19%) address NPS. Of the DTTs, 12 (60%) are small molecules and 8 (40%) are biologics.

In Phase 3, there are 21 trials for repurposed agents (44% of Phase 3 trials) and 12 repurposed agents (39% of Phase 3 agents). Five (42%) repurposed agents are DTTs; all of these are small-molecule DTTs. Two (17%) Phase 3 repurposed agents are putative cognitive enhancing agents, and 5 (42%) Phase 3 repurposed agents are being developed to treat NPS. Nine (19%) Phase 3 trials are long-term extensions of drugs that have completed a prior trial. There are 4 prevention trials in Phase 3. There are 6 trials for MCI/prodromal participants, 13 trials for participants with early AD, 30 trials allowing individuals with mild AD, and 27 trials for participants with moderate or severe AD (categories are not mutually exclusive).

There are 10 new trials in Phase 3. Compared to the last index date (1January 2024), 7 trials were completed, 2 trials were terminated, and 1 trial became of unknown status (no activity on clinicaltrials.gov in the past 2 years).

CADRO categories of AD pathophysiology targeted by at least one drug in current Phase 3 clinical trials include: 11 drugs (35%) target neurotransmitter receptors; 7 treatments (23%) target Aβ-related pathophysiology; 3 agents (10%) address neuroinflammation/immune processes; 2 drugs (7%) each address synaptic plasticity/neuroprotection, metabolism and bioenergetics, and proteostasis/proteinopathy; 1 agent (3%) each targets growth factors and hormones, tau-related processes, and neurogenesis; and 1 agent (3%) is a multi-targeted molecule. In total, 10 CADRO categories are included among target processes for drugs in Phase 3 of the AD drug development pipeline.

The biopharmaceutical industry sponsors 36 (75%) of Phase 3 trials. Biopharmaceutical companies sponsor 6 (50%) of repurposed agents in Phase 3 trials and 24 (67%) of novel, non-repurposed agents in Phase 3 trials.

Review of the global distribution of Phase 3 trials reveals that 4 (9%) are conducted only in North America; 8 (18%) are conducted only outside North America; and 32 (73%) are conducted at both North American and non–North American sites. Four trials did not have site information.

There are four (8% of Phase 3 trials) prevention trials assessing DTTs in the Phase 3 AD pipeline, all are DTT biological agents. The mean treatment exposure time in prevention trials is 211.3 weeks, and they have an estimated recruitment time of 218.8 weeks. The total anticipated duration of a Phase 3 prevention program is 421.5 weeks. These trials have an average of 1269 participants.

There are 44 non-prevention treatment trials in Phase 3, including 15 (34%) trials for DTT small molecules, 10 (23%) trials for DTT biologics, 5 (11%) trials of cognitive enhancers, and 14 (32%) trials for agents addressing NPS. The mean treatment exposure time of Phase 3 small-molecule DTT trials is 54.6 weeks, and they have an estimated recruitment time of 122.2 weeks. The total anticipated duration of DTT small molecule Phase 3 trials is 206.9 weeks. DTT small molecule trials have an average number of 782.5 participants. Phase 3 DTT biologic trials have an average treatment time of 154.2 weeks, a recruitment time of 175.6 weeks, and a total anticipated trial duration of 337.4 weeks. On average, there are 939.1 participants in Phase 3 DTT biologic trials. For cognitive enhancing agents, the mean treatment exposure time is 20 weeks, and they have an estimated recruitment time of 156 weeks. The total anticipated duration of Phase 3 trials for cognitive enhancing agents is 183.8 weeks. Cognitive enhancing agents active in Phase 3 trials have an average number of 267.2 participants. Agents for the treatment of NPS in Phase 3 have a mean treatment exposure of 28 weeks, and they have an estimated recruitment time of 187.6 weeks. The total anticipated duration of Phase 3 trials for NPS treatment is 222.5 weeks. On average, 430.9 individuals participate in the NPS trials.

3.3 | Phase 2 trials

The 2025 AD drug development pipeline includes 86 Phase 2 trials assessing 75 drugs (Table S2; Figure 4). Of the agents in Phase 2, 60 (80%) are DTTs; 11 (15%) target cognitive enhancement; and 4 (5%) address NPS. Of the DTTs, 38 (63%) are small molecules and 22 (37%) are biologics. Thirty-one (41%) Phase 2 agents are repurposed and 40 (47%) Phase 2 trials are for repurposed agents. Twenty-three agents (74% of the repurposed agents) are DTTs including 19 small molecules and 4 biologics. Five Phase 2 drugs (16% of repurposed agents) are putative cognitive enhancing agents, and 3 (10%) are being developed to treat NPS. Seven trials are long-term extensions trials of drugs that had completed a prior trial of the same agent. There are four prevention trials in Phase 2. There are 25 new trials in Phase 2. Compared to the last index date (January 1, 2024), 18 trials were completed, 6 trials were terminated, and 7 trials became of unknown status.

CADRO categories of AD pathophysiology that are targeted by at least one drug in current Phase 2 clinical trials include: 15 agents (20%) address neuroinflammation/immune processes; 12 treatments (16%) target Aβ-related pathophysiology; 12 drugs (16%) pipeline target neurotransmitter receptors; 7 drugs (9%) address synaptic plasticity/neuroprotection and 7 (9%) agents target tau-related processes; 4 therapies (5%) target metabolism and bioenergetics; 3 agents (4%) target each of growth factors and hormones and vascular targets; 2 agents (3%) address oxidative stress; 1 agent (1%) targets each of APOE and related lipid targets, neurogenesis, proteostasis/proteinopathy, gut–brain axis, and circadian rhythm; 3 (4%) are multi-target agents, and 2 (3%) agents had undisclosed targets. In total, 15 CADRO categories are included among target processes for drugs in Phase 2 trials of the AD drug development pipeline.

The biopharmaceutical industry sponsors 43 (50%) Phase 2 trials. Biopharmaceutical companies fund 7 (22%) repurposed agents in Phase 2 trials and 34 (77%) novel, non-repurposed agents in Phase 2.

Review of the global distribution of Phase 2 trials reveals that 40 (49%) are conducted only in North America; 23 (28%) are conducted only outside North America; and 19 (23%) are conducted at both North American and non–North American sites (4 trials did not include this information).

There are four prevention trials in the Phase 2 AD pipeline. Three trials assess DTT small molecules, and one is studying a DTT biologic.

There are 82 non-prevention treatment trials in Phase 2 including 40 DTT small molecule trials (49% of Phase 2 nonprevention trials), 23 (28%) DTT biologics, 12 (15%) trials of cognitive enhancing agents, and 7 (8%) trials of drug addressing NPS. DTT small molecules have a mean treatment exposure duration of 44.9 weeks, and they have an estimated recruitment time of 106.8 weeks. The total anticipated duration of DTT small molecule Phase 2 trials is 172.2 weeks. These trials have an average of 114 participants. DTT biologic trials have treatment periods of 75.7 weeks and recruitment periods of 116.6 weeks. The total anticipated duration of DTT biologic Phase 2 trials is 237.4 weeks. DTT biologics have an average number of participants of 220.1. Cognitive enhancing agents active in Phase 2 trials have a mean treatment exposure time of 29.6 weeks, and they have an estimated recruitment time of 125 weeks. The total anticipated duration of Phase 2 trials for cognitive enhancing agents is 166 weeks. Cognitive enhancer trials have an average number of participants of 151.7. Agents in Phase 2 being developed to ameliorate NPS have a mean treatment exposure time of 12.4

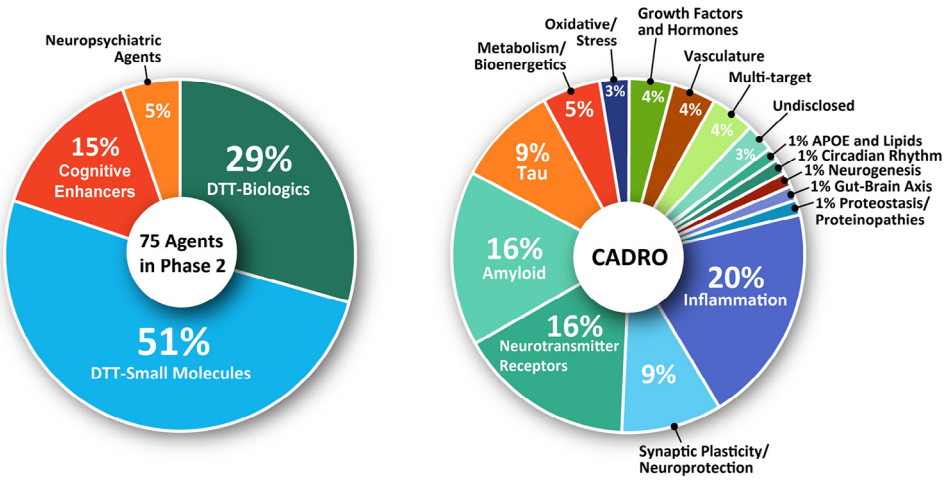

FIGURE 4 Mechanisms of action of agents in Phase 2 Alzheimer clinical trials as classified using 4 categories of therapeutic purpose (left) or the Common Alzheimer's Disease Research Ontology (CADRO) approach (right)((C) figure: J. Cummings; M. de la Flor, PhD, Illustrator).

weeks, and they have an estimated recruitment time of 138.3 weeks. The total anticipated duration of Phase 2 trials for NPS agents is 159.5 weeks. Trials of drugs for treatment of NPS have an average of 188.6 participants.

3.4 | Phase 1 trials

Phase 1 of the 2025 AD drug development pipeline includes 48 trials assessing 45 drugs (Table S3). Of the agents in Phase 1, 33 (73%) are DTTs; 5 (11%) target cognitive enhancement; 6 (13%) address NPS; and 1 has an undisclosed target. Of the DTTs, 15 (45%) are small molecules and 18 (55%) are biologics.

There are seven (15%) repurposed agents in seven Phase 1 trials. Five (71% of repurposed agents) are DTTs, including four small molecules, and one is a DTT biologic. One Phase 1 repurposed agent is a putative cognitive enhancing agent, and one Phase 1 repurposed agent is being developed to treat NPS. There are no Phase 1 long-term extension trials. There are 21 new trials in Phase 1 initiated since the last Index date (January 1, 2024). There are 2 prevention trials and 46 non-prevention trials in Phase 1.

CADRO categories of AD pathophysiology targeted by at least one drug in current Phase 1 clinical trials include: 11 drugs (24%) target Aβ-related pathophysiology; 9 (20%) target neurotransmitter receptors; 7 agents (16%) address neuroinflammation/immune processes and 7 (16%) are tau-related agents; 3 treatments (7%) target metabolism and bioenergetics; there is 1 drug (2%) being assessed for each of the CADRO categories APOE and lipid targets, neurogenesis, oxidative stress, vasculature, growth factors and hormones, synaptic plasticity, and gut–brain axis (1 agent has no declared target). In total, 12 CADRO categories are included among target processes for drugs in Phase 1 trials of the AD drug development pipeline.

The biopharmaceutical industry sponsors 33 (69%) of Phase 1 trials. Biopharmaceutical companies sponsor 31 (79%) of novel, non-repurposed agents in Phase 1 and none of the repurposed agents in Phase 1.

Review of the global distribution of Phase 1 trials reveals that 23 (52%) are conducted only in North America; 16 (36%) are conducted only outside North America; and 5 (11%) are conducted at both North American and non–North American sites (4 trials did not have location information).

Phase 1 trials on clinicaltrials.gov have heterogeneous structures. Some registered trials include only single ascending dose studies, others include only multiple ascending dose studies, and some include both single ascending and multiple ascending studies in the same trial. The mean numbers presented here reflect data concerning Phase 1 trials as they are presented on clinicaltrials.gov.

In the non-prevention trials, Phase 1 small-molecule DTT trials have an average of 8 weeks of treatment, and 81.8 weeks are required for trial recruitment. The total anticipated duration of DTT small-molecule Phase 1 trial programs is 108.2 weeks. Average enrollment in these trials is 61.6 individuals. DTT biologics have a mean treatment exposure time of 33.8 weeks, and they have an average recruitment time of 82.2 weeks. The total anticipated duration of DTT biologic Phase 1 trial programs is 129.2 weeks. The mean enrollment is 53.7 participants. Cognitive enhancing agents active in Phase 1 trials have a mean treatment exposure time of 46.4 weeks, and they have an estimated mean recruitment time of 97.4 weeks. The total anticipated duration of Phase 1 trials for cognitive enhancing agents is 111.1 weeks. The mean enrollment is 68.4 participants. Agents in Phase 1 being developed to ameliorate NPS have a mean treatment exposure of 4.2 weeks, and they have an average recruitment time of 119.5 weeks. The total anticipated duration of Phase 1 trials for NPS treatment is 128.8 weeks. The enrollment is, on average, 55.3 individuals.

3.5 | Biomarkers in trials

Biomarkers play a key role in clinical trials in the 2025 AD drug development pipeline. Among the 182 active AD clinical trials, 104 include a biomarker as an eligibility criterion (57%). Biomarkers may serve as exclusion or inclusion eligibility criteria. The most common eligibility

biomarker is magnetic resonance imaging (MRI), used in 59 trials (32%) usually as an exclusion observation: 9 Phase 1 trials, 32 Phase 2 trials, and 18 Phase 3 trials. Amyloid positron emission tomography (PET) is the second most common biomarker, with 47 trials using these data for eligibility: 7 Phase 1 trials, 29 Phase 2 trials, and 11 Phase 3 trials. Amyloid PET is an inclusion requirement in these trials. Fifty-two (29%) trials used fluid (blood, plasma, serum, or cerebrospinal fluid [CSF]) biomarkers for eligibility. Aβ measures were used in 17 of those trials; 17 trials measured hyperphosphorylated tau (p-tau) in fluid samples.

Across the 182 trials, 50 have a biomarker as a primary outcome measure (27%). The primary outcome biomarkers most often used were amyloid PET and MRI, both with nine trials evaluating the marker. One Phase 1 trial, four Phase 2 trials, and four Phase 3 trials included amyloid PET as an outcome. MRI is used as an outcome in three Phase 1 trials, four Phase 2 trials, and two Phase 3 trials. Twenty-six trials included an imaging biomarker as a primary outcome measure, and 22 assessed fluid samples. As a primary outcome measure, 11 clinical trials evaluated changes in Aβ, with 2 measuring analytes in a fluid sample. When measuring tau pathology, one trial used tau PET and seven used a p-tau biomarker. Total tau and neurofilament light chain (NfL) were included as primary outcome measures in two and three trials, respectively.

3.6 | Trial participants

The total number of participants needed for currently active trials is 50,109. Phase 3 trials require 33,752 participants, accounting for 67% of all participants in current trials. Phase 2 trials require 13,735 participants, and Phase 1 trials require 2802 participants. Trial participants are divided among trials for DTTs (38,859), trials for cognitive enhancing agents (3498), and trials for drugs addressing NPS (7684), reflecting the distribution of types of drugs being assessed in AD trials.

3.7 | Global trial distribution

Phase 3 trials require the largest number of patients and correspondingly the largest number of sites and participating regions. Seventy-three percent of Phase 3 trials include both North American and non–North American sites; 9% are conducted only in North America; and 18% are conducted only outside of North America. Twenty-three percent of Phase 2 trials include both North American and non–North American sites; 49% include only North American sites; 28% of trials are conducted only in non–North American sites. Phase 1 trials are conducted primarily in North America (52%), with fewer conducted without North American sites (non–North American sites only)(36%) or globally (North American and non–North American sites) (1%).

Of DTT small molecule trials, 16% are conducted globally; 50% of trials of DTT biologics trials are conducted globally; 9% of trials for cognitive enhancing agents are global; and 48% of trials for NPS agents are conducted globally.

We assessed the number of trial sites that were identified in at least one AD clinical trial on the Index Date of January 1, 2025. There were 2227 sites identified for North America and 2302 in the rest of the world. We determined how many sites participated in more than one trial. There were 499 North American sites and 443 non–North American sites that were identified in more than one trial on the Index Date.

3.8 | Repurposed agents

There are 46 repurposed agents in the 2025 AD drug development pipeline, comprising 33% of the total number of drugs in trials. Repurposed agents account for 39% of drugs in Phase 3, 41% of drugs in Phase 2, and 16% of drugs in Phase 1. Regarding the therapeutic purpose of agents in the pipeline, 43% of DTT small molecules are repurposed; 10% of biological agents are repurposed; 40% of drugs being assessed for cognitive enhancement are repurposed; and 53% of drugs being assessed for NPS are repurposed.

3.9 | Trial funders

The biopharmaceutical industry funds 62% of all clinical trials in the 2025 AD drug development pipeline. Biopharmaceutical sponsors account for 75% of Phase 3 trials, 50% of Phase 2 trials, and 69% of Phase 1 trials. When therapeutic purpose is considered, 54% of DTT small molecule trials are industry sponsored; 71% of DTT biological agent trials are industry sponsored; 45% of trials of drugs pursuing cognitive enhancement are industry sponsored, and 74% of trials for drugs addressing NPS are industry sponsored. Twenty-eight percent of repurposed agents are industry sponsored (50% of Phase 3 repurposed agents; 22% of Phase 2 repurposed agents; no Phase 1 repurposed agents).

3.10 | Combination therapies

Pharmacodynamic and pharmacokinetic drug combinations are represented in the AD pipeline. There are 20 trials of combination therapies in the 2025 pipeline, comprising 11% (20/182) of all current trials. Ten trials test pharmacodynamic combinations (both agents are posited to have pharmacodynamic effects) that address aspects of inflammation or Aβ pathophysiology. Two of these trials use the senolytic combination of dasatinib plus quercetin to target neuroinflammation.

There are 10 trials for pharmacokinetic combinations(one agent is present to optimize the dose of the other) in trials in the current AD pipeline. In these combinations, the active ingredient is paired with a drug that reduces peripheral side effects or reduces peripheral metabolism. There are six trials assessing pharmacokinetic combinations of dextromethorphan and a CYP2D6 inhibitor to prevent the hepatic metabolism of dextromethorphan and facilitate more entry of active drug into the central nervous system (CNS). The agents

in these trials target the reduction of agitation in AD dementia. There are four trials of xanomeline plus trospium. In this combination, trospium reduces dose-limiting peripheral cholinergic side effects, allowing higher doses of xanomeline to be administered with enhanced opportunity for CNS entry and therapeutic benefit. These trials target the amelioration of psychosis associated with AD dementia.

3.11 | Drugs scheduled to complete Phase 3 and Phase 2 trials in 2025

Completion and reporting of Phase 2 and Phase 3 trials in 2025 will provide important information on specific agents as well as target processes and pathways. Twelve drugs are anticipated to complete Phase 3 trials in 2025, including dextromethorphan plus quinidine, nabilone, semaglutide, simufilam, nilotinib, piromelatine, masupirdine, AR1001, xanomeline plus trospium, valiltramiprosate, rotigotine + rivastigmine, and dextromethorphan + bupropion (Table S1). Twenty-nine trials are scheduled to complete Phase 2 in 2025 and will provide information on an array of targets and mechanisms (Table S2).

4 | DISCUSSION

This analysis of the AD drug development pipeline shows a robust level of activity with 182 clinical trials assessing 138 candidate treatments. This compares to 164 trials assessing 127 agents in the 2024 AD pipeline.[10] There has been a marked increase in Phase 1 activity with nearly twice as many trials (48 vs. 26) and drugs (45 vs. 25) in 2025 compared to 2024.

A plethora of pathophysiological processes are being addressed by candidate agents in the pipeline; 15 CADRO processes are targeted for therapeutic intervention. There have been small changes in the number of agents populating the CADRO categories in 2025 compared to 2024. There are more agents addressing tau (+4), Aβ (+2), neurotransmitter receptors (+2), vasculature (+1), growth factors and hormones (+1), and gut–brain axis (+1). There are fewer agents addressing synaptic plasticity and neuroprotection (−6), APOE and lipids (−3), circadian rhythm (−2), neurogenesis (−1), inflammation (−1), proteostasis/proteinothies (−1), and epigenetics (−1). The canonical targets of Aβ and tau account for 29% of agents in the pipeline (18% and 11%, respectively).

There are an approximately equal number of clinical trial sites represented in the 2025 pipeline in North America (2227 sites) as in the rest of the world (2302 sites). Most of these sites (approximately 80%) participated in only one trial; 499 North American sites and 443 non–North American sites participated in more than one trial. Global Burden of Disease data show that 10% of patients with dementia (most ascribed to AD) live in North America.[12] Increasing the number of trial sites in non–North American regions might allow the acceleration of participant recruitment and expand the demographic characteristics of participants in clinical trial cohorts to provide a better representation of the patients who will ultimately be treated with the therapeutic agents under study. This will enable a more informed understanding of the biological heterogeneity of AD, improve the generalizability of trial outcomes, and facilitate a precision medicine approach to care in clinical practice.based

An increase in the number of trials per site might allow for a decrease in the total number of sites and increase operational efficiencies.

Repurposing is a developmental pathway that plays an important role in the 2025 AD pipeline. The relatively high percentage of DTT small molecules (43%) and drugs being developed for the amelioration of NPS (53%) that are repurposed indicates a substantial dependence on drug repurposing for the development of orally available DTTs and NPS therapies.

Trial innovation is evident in the 2025 AD drug development pipeline. For example, plasma biomarkers have a greater role in AD diagnosis. Several trials entering the pipeline this year use plasma p-tau 217 to confirm the diagnosis of AD and function as an eligibility criterion for clinical trial participation (NCT06677203; NCT66531534); one trial based eligibility on the basis of Aβ 42/40 plus the ratio of p-tau 217/non-phosphorylated tau 217 (NCT05891496); one trial used "blood biomarkers" or past CSF or PET evidence of Aβ abnormalities (NCT06653153).[13] Recent studies suggest that plasma p-tau 217 measures are equivalent in diagnostic accuracy to CSF biomarkers of AD pathology.[3,14] CSF microtubule binding region (MTBR) tau243 levels have a high correlation with insoluble tau observed with tau PET and are used in a trial of anti-tau antibody as a primary outcome measure (NCT06602258).[15] Two trials of immunologic agents use translocator protein (TSPO) PET as outcome measures (NCT06745583, FEPPA; NCT06489548, PBR06 PET).[16]

In summary, growth in the number of trials and agents, the robust diversity of targets of drugs in the 2025 AD pipeline, and the notable increase in Phase 1 activity demonstrate momentum toward identifying new therapies for the treatment of AD. The use of biomarkers to determine eligibility and as outcomes in clinical trials shows the increasingly important role that biomarkers play in AD drug development. Pharmaceutical companies account for over half of all drugs in the pipeline and 75% of drugs in Phase 3. Many patients (more than 50,000) are needed to populate currently active clinical trials. Increasing the number of clinical trial sites may enhance recruitment, particularly if the sites are in areas with higher numbers of patients with AD. Increasing the number of trials per site might also enhance recruitment, improve operational efficiency, and increase the quality of site performance. Overall, the 2025 AD pipeline demonstrates growth and innovation in the quest to find more and better treatments for patients with AD.

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CONFLICT OF INTEREST STATEMENT

J.L.C. has provided consultation to Acadia, Acumen, ALZpath, Annovis, Aprinoia, Artery, Axsome, Biogen, Biohaven, BioXcel, Bristol-Myers Squib, Cervomed, Eisai, Fosun, GAP Foundation, Green Valley, IGC, Janssen, Kinoxis, Lighthouse, Lilly, Lundbeck, LSP/eqt, Mangrove Therapeutics, Merck, MoCA Cognition, New Amsterdam, Novo Nordisk, NSC Therapeutics, Optoceutics, Otsuka, Oxford Brain Diagnostics, Praxis, Prothena, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, sinaptica, T-Neuro, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies. G.L. is a full-time employee of Eisai Co., Ltd. K.Z. is CEO of CNS Innovations. Y.Z., J.F., A. L.-O., and F.C. declare no competing interests. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All data are from an anonymized publicly available clinical trial registry (clinicaltrials.gov). No individual participant-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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