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## Alzheimer's Disease Drug Development Pipeline: 2020

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## RESEARCH ARTICLE

## Alzheimer's disease drug development pipeline: 2020

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**Abstract**

**Introduction:** Alzheimer's disease (AD) is a growing public health concern affecting millions of patients worldwide and costing billions of dollars annually. We review the pipeline of drugs and biologics in clinical trials for the treatment of AD. We use the Common Alzheimer's and Related Dementias Research Ontology (CADRO) to classify treatment targets and mechanisms of action. We review our annual pipeline reports for the past 5 years to provide longitudinal insight into clinical trials and drug development for AD.

**Methods:** We reviewed ClinicalTrials.gov as of February 27, 2020, and identified all trials of pharmacologic agents currently being developed for treatment of AD as represented on this widely used U.S. Food and Drug Administration registry.

**Results:** There are 121 agents in clinical trials for the treatment of AD. Twenty-nine agents are in 36 Phase 3 trials, 65 agents are in 73 Phase 2 trials, and 27 agents are in 27 Phase 1 trials. Twelve agents in trials target cognitive enhancement and 12 are intended to treat neuropsychiatric and behavioral symptoms. There are 97 agents in disease modification trials. Compared to the 2019 pipeline, there is an increase in the number of disease-modifying agents targeting pathways other than amyloid or tau.

**Discussion:** The 2020 pipeline has innovations in clinical trials and treatment targets that provide hope for greater success in AD drug development programs. Review of clinical trials over the past 5 years show that there is progressive emphasis on non-amyloid targets, including candidate treatments for inflammation, synapse and neuronal protection, vascular factors, neurogenesis, and epigenetic interventions. There has been a marked growth in repurposed agents in the pipeline.

**KEYWORDS**

Alzheimer's disease, biomarkers, clinical trials, Common Alzheimer's and Related Dementias Research Ontology (CADRO), drug development, NIH, pharmaceutical companies, repurposed drugs

**1 | INTRODUCTION**

Alzheimer's disease (AD) is a progressive neurodegenerative disease that currently produces dementia in 5.8 million U.S. citizens and this

number will increase to 13.5 million by 2050.<sup>1</sup> AD dementia is projected to have a devastating impact on global populations by 2050 with 131 million affected. The costs of AD are accelerating—rising from \$1 trillion globally in 2018 to a projected \$2 trillion in 2030.<sup>2</sup> Means of

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preventing, delaying the onset, slowing the progression, and improving the symptoms of AD are urgently needed. This annual review describes the pipeline of drugs in development for AD; discusses innovations in drug development; and provides an update on new targets, drugs, and biomarkers represented in current clinical trials. We call attention to notable recent advances in the field.

This is the 5th year of the pipeline review, presenting an opportunity to describe changes in AD drug development from a longitudinal perspective.<sup>3-6</sup> To better present the targets of AD therapeutics in this review, we adopted the terminology of the Common Alzheimer's and Related Dementias Research Ontology (CADRO).<sup>7,8</sup> The CADRO identifies the following potential targets for AD from early-stage to late-stage clinical drug development: amyloid, tau, apolipoprotein E (apoE)/lipids/lipoprotein receptors, neurotransmitter receptors, neurogenesis, inflammation, oxidative stress, cell death, proteostasis/proteinopathies, metabolism/bioenergetics, vasculature, growth factors/hormones, synaptic plasticity/neuroprotection, epigenetics, and "others." While this classification was not conceived primarily as a means of capturing drug mechanisms, the CADRO systematizes the processes of AD that are the current drug targets relevant to AD and provides a framework for classifying treatment mechanisms. We reclassified the drug mechanisms from previous reviews using the CADRO approach. Some agents have more than one mechanism of action and, in these cases, we noted both mechanisms and depended on the available literature to identify a dominant mechanism. Infection and immunity were not included in the original CADRO system and we included any agents targeting infection or immunity with inflammation for the purpose of this review. We kept the terminology of "symptomatic" treatments for agents whose purpose was cognitive enhancement or control of neuropsychiatric symptoms without claiming to impact the biological causes of cell death in AD, and we used "disease-modifying" for treatments intended to change the biology of AD and produce neuroprotection (often through a variety of intermediate mechanisms such as effects on amyloid or tau).<sup>9,10</sup> AD is now recognized to have preclinical, prodromal, and dementia phases,<sup>11</sup> and we note if the studies are prevention trials including cognitively normal participants with preclinical AD; prodromal trials involving participants with mild cognitive impairment (MCI) but not meeting criteria for dementia; or treatment trials for participants with mild, moderate, or severe AD dementia.

## 2 | METHODS

The U.S. Food and Drug Administration (FDA) website ClinicalTrials.gov is the source of information for this review. The "Common Rule" governing ClinicalTrials.gov requires registration on this site of all trials from sponsors with an investigational new drug (IND) or investigational new device (IDE) being assessed in the United States. Compliance with the required trial registration is high among trial sponsors.<sup>12-15</sup> There are other clinical trial registries with some treatments not present on the ClinicalTrials.gov website, and our review is not an exhaustive listing of every clinical trial or every drug in trials for the treatment of AD. The United States has more clinical

### HIGHLIGHTS

- In 2020, there are 121 unique therapies in clinical trials for Alzheimer's disease (AD) as registered on clinicaltrials.gov.
- The largest number of drugs in the AD pipeline are putative disease-modifying agents targeting disease onset or progression.
- There is a growing number of repurposed agents (approved from non-AD indication) in the pipeline; repurposed agents now comprise 43% of the pipeline.
- The total number of participants required for currently recruiting trials is 31,314.

### RESEARCH IN CONTEXT

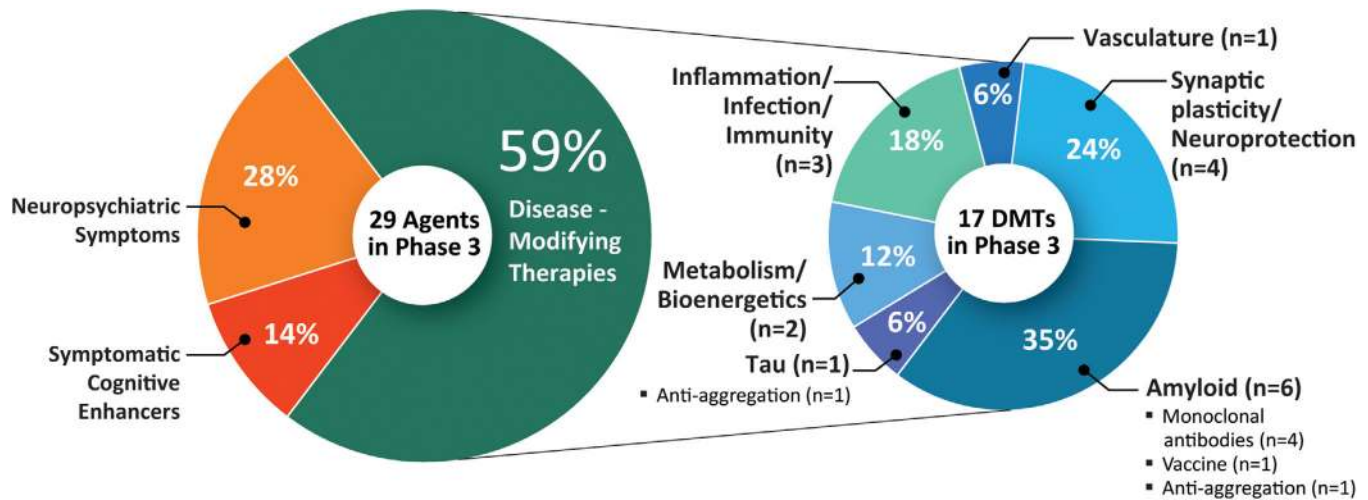
1. Systematic review: We reviewed all drugs currently in clinical trials for Alzheimer's disease (AD) listed in the federal government database, ClinicalTrials.gov.
2. Interpretation: There are 121 agents in clinical trials for the treatment for AD. Ninety-seven of these drugs are disease-modifying agents intended to change the underlying biology of AD. Twelve of the drugs are putative cognitive enhancing agents, and 12 are being developed for the treatment of neuropsychiatric symptoms. Over the past 5 years, there has been an increase in the number of disease-modification treatment candidates, greater diversification of the targets for drugs in the pipeline, more repurposed agents, and greater integration of biomarkers into development programs.
3. Future directions: Progress is occurring in new drug development for AD with potential new treatments for cognitive decline, insomnia, and psychosis. Trial methodology is being advanced, improved biomarkers to report on drug effects are emerging, and novel outcomes and designs reflect innovations that are assisting in development of new treatments for AD.

trials than any other nation; ClinicalTrials.gov includes the majority of agents currently in clinical trials for AD globally. Phase 1 trials are often conducted outside the United States and may not be captured on clinicaltrials.gov. Comparison to the World Health Organization registry suggests that clinicaltrials.gov includes 90% of worldwide Phase 3 trials; 86% of global Phase 2 trials; 43% of Phase 1 trials.

This pipeline report is based on trials present on ClinicalTrials.gov as of February 27, 2020; the tables and text of the review apply to the information available at that time. On average, clinical trial results are published in peer-reviewed literature 25 months after completion of the trial,<sup>16</sup> and in our discussion we include recently published trial results of agents previously noted to be in the pipeline. We include







**FIGURE 2** Mechanisms of action of agents in Phase 3 of the Alzheimer's disease drug development pipeline (ClinicalTrials.gov accessed February 27, 2020) (Figure by Mike de la Flor)

Phase 1, Phase 1/2, Phase 2, Phase 2/3, and Phase 3. Most Phase 1 trials include healthy participants and some trials list "healthy" as the condition/disease rather than listing both "Alzheimer's" and "healthy." These trials may have escaped capture in our search.

Drug targets and mechanisms of action (MOA) are important aspects of this review. MOA of listed agents was determined from the information on ClinicalTrials.gov or from a comprehensive literature search. In a few cases, the mechanism is undisclosed and could not be identified in the literature; we note these agents as having an "unknown" or "undisclosed" MOA. We grouped the mechanisms into symptomatic agents or disease-modifying therapies (DMTs). We divided the symptomatic agents into those that are putative cognitive enhancing agents or those that address neuropsychiatric and behavioral symptoms. DMTs were divided into small molecules or biologics, including immunotherapies. DMTs were further categorized using the CADRO system. The distinction between symptomatic and disease-modifying agents can be arbitrary, and some agents may have both properties. For purposes of this review, we chose what appears to be the principal MOA.

## 3 | RESULTS

### 3.1 | Overview

As of February 27, 2020, there were 121 agents in 136 trials of AD therapies. Figure 1 shows all pharmacologic compounds currently in clinical trials for AD. Twelve (9.9%) agents in trials target cognitive enhancement and 12 (9.9%) are intended to treat neuropsychiatric and behavioral symptoms. There are 97 (80.2%) agents that intend to achieve disease modification; 16 (16.5%) of these have amyloid and 11 (11.3%) have tau as the primary target or as one of several effects seen in non-clinical or previous clinical studies. Six of the anti-amyloid agents are small molecules and ten are monoclonal antibodies or biological

therapies. Anti-tau agents include four small molecules and seven biologics.

### 3.2 | Phase 3

In Phase 3 there are 29 agents in 36 trials (Figures 1 and 2, Table 1). There are 12 symptomatic agents (41%) in Phase 3; 4 cognitive enhancers (13.8%) and 8 targeting behavioral symptoms (27.6%). Of the 17 (59%) putative disease-modifying agents in Phase 3, there are 5 biological therapies and 12 oral agents/small molecules. All five of the biological therapies, and one of the small molecules have amyloid as the primary or one of several targets (35.3% of DMTs). Other CADRO mechanisms represented among Phase 3 DMT molecules include tau ( $n = 1$ ; 5.9%), inflammation/infection/immunity ( $n = 3$ ; 17.6%), metabolism and bioenergetics ( $n = 2$ ; 11.8%), vasculature ( $n = 2$ ; 5.9%), and synaptic plasticity/neuroprotection ( $n = 4$ ; 23.5%). Of the drugs with amyloid targets, there were five immunotherapies and one anti-aggregation agent. Figure 2 shows the MOAs of agents in Phase 3. Six (35%) of the DMT agents are repurposed agents approved for use in another indication.<sup>17-19</sup> There are five new agents in the Phase 3 pipeline compared to 2019.

In Phase 3, there are 4 prevention trials enrolling cognitively normal participants; 11 trials enrolling participants with prodromal AD/MCI or prodromal-to-mild AD; 1 trial enrolling both cognitively normal patients and patients with MCI to mild AD; 11 trials of patients with mild-to-moderate AD; and 9 trials of patients with mild-to-severe AD.

Phase 3 trials included a mean of 554 participants and had a mean duration of 240 weeks (including the recruitment and the treatment period). The mean treatment exposure period was 64 weeks. DMT trials were longer and larger than trials of symptomatic agents with a mean duration of 279 weeks comprising 98 treatment weeks and including an average of 689 participants. The mean duration of cognitive enhancer trials was 162 weeks (19 treatment weeks), and they

**TABLE 1** Agents in Phase 3 of Alzheimer's disease drug development (ClinicalTrials.gov accessed February 27, 2020)

Agent	CADROmechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
Aducanumab	Amyloid	Monoclonal antibody directed at plaques and oligomers	Remove amyloid (DMT)	Not yet recruiting (NCT04241068)	Biogen	Mar 2020	Sep 2023
AGB101 (low-dose levetiracetam)	Synaptic plasticity/ neuroprotection	SV2A modulator	Improve synaptic function; reduce amyloid-induced neuronal hyperactivity (DMT)	Recruiting (NCT03486938)	AgeneBio, NIA	Jan 2019	Nov 2022
ALZT-OP1 (cromolyn + ibuprofen)	Inflammation	Mast cell stabilizer (cromolyn), anti-inflammatory (ibuprofen)	Microglial modulation; promote microglial clearance of amyloid (DMT)	Active, not recruiting (NCT02547818)	AZTherapies	Sep 2015	Dec 2020
ANAVEX2-73 (blarcamesine)	Synaptic plasticity/ neuroprotection	Sigma-1 receptor agonist, M2 autoreceptor antagonist	Enhances cell signaling to ameliorate oxidative stress, protein misfolding, mitochondrial dysfunction and inflammation (DMT)	Recruiting <sup>a</sup> (NCT037	Anavex life sciences	Jul 2018	Dec 2021
AVP-786	Neurotransmitter receptors	Sigma 1 receptor agonist; NMDA receptor antagonist	Improve neuropsychiatric symptoms (agitation)	Recruiting (NCT03393520)	Avanir	Oct 2017	Jun 2021
				Recruiting, extension study (NCT02446132)	Avanir	Dec 2015	Jun 2022
AXS-05	Neurotransmitter receptors	Sigma 1 receptor agonist; NMDA receptor antagonist (dextromethorphan); dopamine-norepinephrine reuptake inhibitor (bupropion)	Improve neuropsychiatric symptoms (agitation)	Recruiting <sup>a</sup> (NCT03226522)	Axsome therapeutics	Jul 2017	Jun 2020
Azeliragon	Amyloid, inflammation	RAGE antagonist	Reduce amyloid transport into the brain; reduce inflammation (DMT)	Recruiting <sup>a</sup> (NCT039	vTv Therapeutics	Jun 2019	Jul 2023
BAN2401	Amyloid	Monoclonal antibody directed at protofibrils	Reduce protofibrillar amyloid and amyloid plaques (DMT)	Recruiting (NCT03887455)	Eisai, Biogen	Mar 2019	Mar 2024

(Continues)

**TABLE 1** (Continued)

Agent	CADROmechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
BHV4157 (troriluzole)	Synaptic plasticity/ neuroprotection	Glutamate modulator; prodrug of riluzole	Reduce synaptic levels of glutamate; improve synaptic functioning (DMT)	Active, not recruiting <sup>a</sup> (NCT03605667)	Biohaven pharma, ADCS	Jul 2018	Dec 2020
BPDO-1603	Undisclosed	Undisclosed	Undefined mechanism (cognitive enhancer)	Not yet recruiting (NCT04229927)	Hyundai pharmaceutical	Feb 2020	Mar 2023
Brexipiprazole	Neurotransmitter Receptors	D2 receptor partial agonist, serotonin-dopamine modulator	Improve neuropsychiatric symptoms (agitation)	Recruiting <sup>a</sup> (NCT03620981)	Otsuka	Aug 2018	Nov 2021
				Recruiting, extension study (NCT03594123)	Otsuka	Oct 2018	Aug 2021
				Recruiting (NCT03548584)	Otsuka	May 2018	Dec 2020
				Recruiting, extension study (NCT03724942)	Otsuka	Nov 2018	May 2021
CAD106 <sup>b</sup>	Amyloid	Amyloid vaccine	Remove amyloid (DMT)	Active, not recruiting <sup>a</sup> (NCT02565511)	Novartis, Amgen, NIA, Alzheimer's Association, Banner Alzheimer's Institute	Nov 2015	Mar 2025
COR388	Inflammation/infection	Bacterial protease inhibitor targeting gingipain produced by <i>P. gingivalis</i>	Reduce neuroinflammation and hippocampal degeneration (DMT)	Recruiting <sup>a</sup> (NCT038)	Cortexyme	Mar 2019	Dec 2022
Escitalopram	Neurotransmitter receptors	SSRI	Improve neuropsychiatric symptoms (agitation)	Recruiting (NCT03108846)	Johns Hopkins University, NIA	Jan 2018	Aug 2022
Gantenerumab	Amyloid	Monoclonal antibody directed at plaques and oligomers	Remove amyloid (DMT)	Active, not recruiting (NCT02051608)	Roche	Mar 2014	Apr 2021
				Active, not recruiting (NCT01224106)	Roche	Nov 2010	Aug 2020
				Recruiting (NCT03444870)	Roche	Jun 2018	May 2023
				Recruiting (NCT03443973)	Roche	Aug 2018	May 2023

(Continues)

**TABLE 1** (Continued)

Agent	CADROmechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
Gantenerumab and solanezumab	Amyloid	Monoclonal antibody directed at plaques and oligomers (gantenerumab); Monoclonal antibody directed at monomers (soltanezumab)	Remove amyloid; reduce amyloid production (DMT)	Recruiting <sup>ac</sup> (NCT01760015)	Washington University, Eli Lilly, Roche, NIA, Alzheimer's Association	Dec 2012	Mar 2021
Ginkgo biloba	Metabolism and bioenergetics	Plant extract with antioxidant properties	Improve brain blood flow and mitochondrial function (cognitive enhancer)	Recruiting <sup>b</sup> (NCT03090118)	Nanjing Medical University	Aug 2016	Mar 2020
Guanfacine	Neurotransmitter receptors	Alpha-2 adrenergic agonist	Modulation of noradrenergic deficit (cognitive enhancer)	Recruiting (NCT03116126)	Imperial College London, UK National Institute of Health Research	Jan 2019	Mar 2021
Icosapent ethyl (IPE)	Synaptic plasticity/ neuroprotection	Purified form of the omega-3 fatty acid EPA	Improve synaptic function; reduce inflammation (DMT)	Recruiting <sup>b</sup> (NCT02711111)	VA Office of Research and Development, University of Wisconsin, Madison	Jun 2017	Nov 2021
Losartan and amlodipine and atorvastatin + exercise	Vasculature	Angiotensin II receptor blocker (losartan), calcium channel blocker (amlodipine), cholesterol agent (atorvastatin)	Vascular risk reduction; preservation of cognitive function (DMT)	Active, not recruiting <sup>b</sup> (NCT02913664)	University of Texas Southwestern	Sep 2016	Mar 2022
Masitinib	Inflammation/immunity	Tyrosine kinase inhibitor	Modulation of mast cell-related inflammatory processes; reduce amyloid protein and tau phosphorylation (DMT)	Active, not recruiting (NCT01872598)	AB Science	Jan 2012	Dec 2019
Metformin	Metabolism and bioenergetics	Insulin sensitizer	Improve CNS glucose metabolism (DMT)	Not yet recruiting <sup>b</sup> (NCT04098666)	Columbia University, NIA, EMD Serono	Apr 2020	Apr 2024
Methylphenidate	Neurotransmitter receptors	Dopamine reuptake inhibitor	Improve neuropsychiatric symptoms (apathy)	Active, not recruiting (NCT02346201)	Johns Hopkins University, NIA	Jan 2016	Jun 2020

(Continues)



**TABLE 1** (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
Mirtazapine	Neurotransmitter Receptors	Alpha-1 antagonist	Improve neuropsychiatric symptoms (agitation)	Recruiting (NCT03031184)	University of Sussex	Jan 2017	Jul 2020
Octahydro-aminoacridine Succinate	Neurotransmitter receptors	Acetylcholinesterase inhibitor	Improve acetylcholine signaling (cognitive enhancer)	Recruiting (NCT03283059)	Shanghai Mental Health Center, Changchun-Huayang High-tech, Jiangsu Shenyang High-tech	Aug 2017	Feb 2021
Solanezumab	Amyloid	Monoclonal antibody directed at monomers	Remove amyloid and prevent aggregation (DMT)	Active, not recruiting (NCT02008357)	Eli Lilly, ATRI	Feb 2014	Jul 2022
Tricaprilin	Metabolism and bioenergetics	Ketone body stimulant; caprylic triglyceride	Induce ketosis to improve mitochondrial function and neuronal metabolism (DMT)	Not yet recruiting (NCT04187547)	Cerecin	Jul 2020	Dec 2022
TRx0237 (LMTX)	Tau	Tau protein aggregation inhibitor	Reduce tau mediated neuronal damage (DMT)	Recruiting (NCT03446001)	TauRx Therapeutics	Jan 2018	Dec 2022
Zolpidem and zopiclone	Neurotransmitter receptors	Positive allosteric modulator of GABA-A receptors	Improve neuropsychiatric symptoms (sleep disorders)	Recruiting (NCT03075241)	Brasilia University Hospital	Oct 2016	Dec 2020

Abbreviations: ADCS, Alzheimer's disease cooperative study; ATRI, Alzheimer's Therapeutic Research Institute; BACE, beta-site amyloid precursor protein cleaving enzyme; CADRO, Common Alzheimer's Disease and Related Disorders Research Ontology; DMT, disease-modifying therapy; EPA, eicosapentaenoic acid; GABA, gamma-aminobutyric acid; NIA, National Institute on Aging; SSRI, selective serotonin reuptake inhibitor; SV2A, synaptic vesicle protein 2A  
Note: Twenty-nine agents in 36 Phase 3 clinical trials currently ongoing as of February 27, 2020 according to ClinicalTrials.gov.

Note: Bolded terms represent new agents into the 2020 Phase 3 pipeline since 2019.

Note: The following agents have been identified as terminated per company press releases and have been removed from the current pipeline although they are still listed as ongoing on ClinicalTrials.gov: CNP520/umibecestat (NCT03131453), E2609/elenbecestat (NCT02956486, NCT03036280).

<sup>a</sup>Phase 2/3 trials.

<sup>b</sup>CNP520 (umibecestat) has been removed from the GENERATION 1 trial.

<sup>c</sup>DIAN-TU trial has been completed and failed to meet its clinical outcomes for both gantenerumab and solanezumab. Secondary analyses are pending.

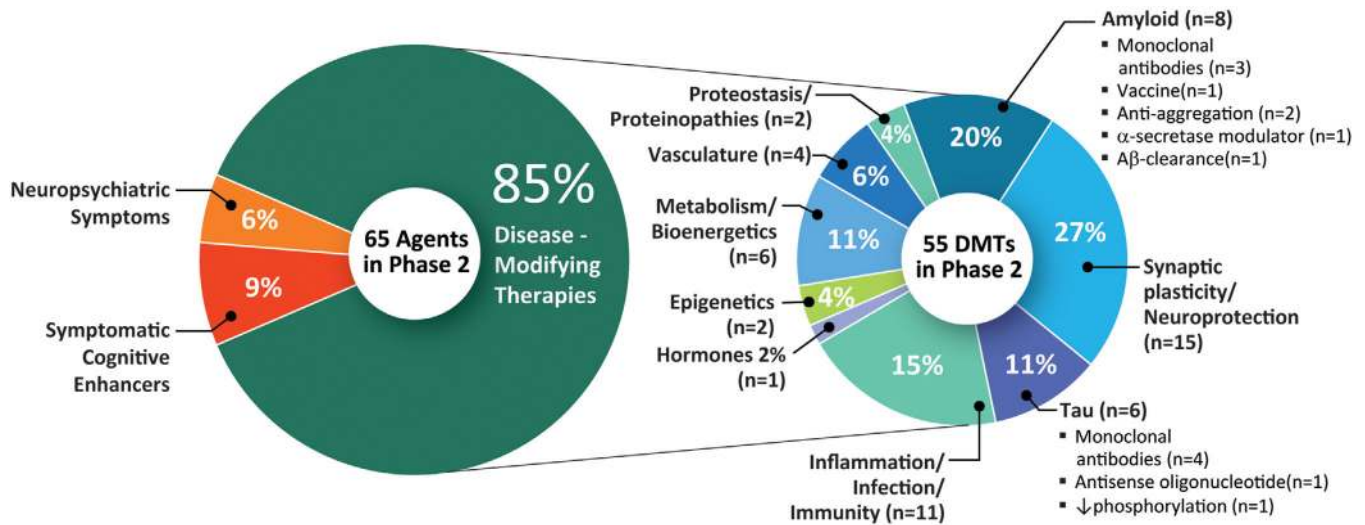
included an average of 428 participants. Trials of agents for behavioral symptoms had a mean duration of 193 weeks (15 treatment weeks) and included a mean of 342 subjects. For the average DMT trial, the recruitment period (average 160 weeks) substantially exceeds the exposure period (average 98 weeks) indicating that drug development timelines are more related to the success of recruitment than to the period required to assess the efficacy and safety of the agent.

When examined by trial population, DMT prevention trials are 375 weeks in duration (178 treatment weeks); trials for patients with

MCI/prodromal/prodromal-to-mild AD are 275 weeks in duration (99 treatment weeks); and trials for patients with mild to moderate AD are 223 weeks in duration (38 treatment weeks).

### 3.3 | Phase 2

Phase 2 has a larger number of therapies with more diverse mechanisms that are being assessed compared to the Phase 3 repertoire of agents. There are 65 agents in 73 trials (Figure 1 and 3, Table 2).



**FIGURE 3** Mechanisms of action of agents in Phase 2 of the Alzheimer's disease drug development pipeline (ClinicalTrials.gov accessed February 27, 2020)(Figure by Mike de la Flor)

Of these, there are ten symptomatic agents: six cognitive enhancers and four agents targeting behavioral symptoms. There are 55 potential DMTs in Phase 2 trials; 14 biologics and 41 small molecules. Four of the small molecules and four of the biologics have amyloid reduction as one of the mechanisms observed in non-clinical studies (14.5% of DMTs). One small molecule and five biologics in Phase 2 target tau-related processes as one of their mechanisms (10.9% of DMTs). There are 15 small molecules with synaptic plasticity/neuroprotection as one of the mechanisms (27.3% of DMTs). Four of the biologics and seven of the small molecules have inflammation/infection/immunity as their mechanism (20% of DMTs). Among other CADRO mechanisms represented in Phase 2, there were two agents targeting proteostasis/proteinopathies, six agents with metabolism and bioenergetic targets, four agents addressing vascular factors, one hormonal agent, and two epigenetic agents. Of the drugs with amyloid targets, there were four immunotherapies, two anti-aggregation agents, one alpha-secretase modulator, and one involving amyloid clearance. Figure 3 shows the MOAs of agents in Phase 2. There are five trials involving stem cell therapies in Phase 2 (see Table 4). Twenty-three (42%) of the Phase 2 DMT candidates are repurposed agents approved for use in another indication. There are 14 new agents in the Phase 2 pipeline compared to 2019.

Two of the Phase 2 trials were prevention trials; 37 trials involved patients with MCI/prodromal or prodromal-to-mild AD; 32 were trials for mild-to-moderate AD; one trial was for patients with severe AD; and one trial included patients with mild-to-severe AD.

Phase 2 trials are shorter in duration and smaller in terms of participant number than Phase 3 trials. Phase 2 trials had a mean duration of 192 weeks, average treatment period of 43 weeks and included an average of 131 subjects in each trial. Phase 2 trials of DMTs had a mean duration of 201 weeks, average treatment period of 45 weeks, and included an average of 137 subjects in each trial.

### 3.4 | Phase 1

Phase 1 has 27 agents in 27 trials (Figure 1, Table 3). There are two cognitive enhancers being assessed in Phase 1 and no agents addressing neuropsychiatric symptoms. There are 18 DMT small molecules and 7 DMT biologics being assessed in Phase 1. One of the small molecules and one of the biologics have amyloid as a primary target or one among several targets. Tau is targeted by two small molecules and two biologics in Phase 1 studies. Other CADRO mechanisms represented in Phase 1 include targeting inflammation/infection/immunity ( $n = 6$ ), metabolism/bioenergetics ( $n = 3$ ), growth factors/hormones ( $n = 2$ ), epigenetics ( $n = 3$ ), neurogenesis ( $n = 1$ ), vasculature ( $n = 1$ ), synaptic plasticity/neuroprotection ( $n = 1$ ), and combination of metabolism/bioenergetics and vasculature ( $n = 2$ ) as the primary or one of a combination of effects. There are two stem cell therapy trials in Phase 1 (Table 4).

Phase 1 trials have an average duration of 116 weeks (recruitment and treatment period) and include a mean number of 43 participants in each trial.

### 3.5 | Trial sponsors

Across all trials, 46% are sponsored by the biopharma industry, 39% by academic medical centers (with funding from NIH, industry, and/or other entities), and 15% by others. Table 5 shows the sponsor of agents in each phase of development.

Repurposed agents have promise to accelerate drug development because the results of non-clinical studies, dosing, safety, tolerability, formulation, manufacturing, and distribution are known.<sup>17-19</sup> Of the 57 trials for 52 repurposed agents across all phases, 9 trials (16%) are by the biopharma industry, 42 trials (74%) are hosted by

**TABLE 2** Agents in Phase 2 of Alzheimer's disease drug development (ClinicalTrials.gov accessed February 27, 2020)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
ABBV-8E12	Tau	Monoclonal antibody	Remove tau and prevent tau propagation (DMT)	Active, not recruiting (NCT02880956)	AbbVie	Oct 2016	Jul 2021
				Recruiting, extension study (NCT03712787)		Mar 2019	Aug 2026
ABvac40	Amyloid	Active immunotherapy	Remove amyloid (DMT)	Recruiting (NCT03461276)	Araclon biotech	Feb 2018	Feb 2022
AD-35	Neurotransmitter Receptors	Acetylcholinesterase inhibitor	Improve acetylcholine signaling (cognitive enhancer)	Recruiting (NCT03625401)	Zhejiang hisun pharmaceutical	Oct 2018	Jul 2020
				Active, not recruiting (NCT03790982)		Zhejiang hisun pharmaceutical	Dec 2018
AMX0035	Neuroprotection, cell death	Combination of sodium phenylbutyrate and tauroursodeoxycholic acid	Reduce cell death associated with mitochondrial dysfunction; modulate neuroinflammation (DMT)	Recruiting (NCT03533257)	Amylyx pharmaceuticals, ADDF, Alzheimer's association	Aug 2018	Sep 2020
ANAVEX 2-73 (blarcamesine)	Synaptic plasticity/ Neuroprotection	Sigma-1 receptor agonist; M2 autoreceptor antagonist	Enhance cell signaling to ameliorate oxidative stress, protein misfolding, mitochondrial dysfunction and inflammation (DMT)	Active, not recruiting, extension study (NCT02756858)	Anavex life sciences	Mar 2016	Nov 2020
APH-1105	Amyloid	Alpha-secretase modulator	Reduce amyloid (DMT)	Not yet recruiting (NCT03806478)	Aphios	Jun 2021	Dec 2022
AR1001	Synaptic plasticity/ neuroprotection	PDE-5 inhibitor	Improve synaptic plasticity (DMT)	Recruiting (NCT03625622)	AriBio Co.	Jan 2019	Aug 2020
BAN2401	Amyloid	Monoclonal antibody directed at protofibrils	Remove amyloid protofibrils and reduce amyloid plaques (DMT)	Active, not recruiting (NCT01767311)	Eisai	Dec 2012	Jul 2022
Benfotiamine	Metabolism and bioenergetics	Synthetic thiamine	Improve glucose use (DMT)	Active, not recruiting (NCT02292238)	Burke Medical Research Institute, Columbia University, NIA, ADDF	Nov 2014	Nov 2019
BIIB092	Tau	Monoclonal antibody targeting truncated form of tau	Remove tau and reduce tau propagation (DMT)	Active, not recruiting (NCT03352557)	Biogen	May 2018	Mar 2024

(Continues)

**TABLE 2** (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
BPN14770	Synaptic plasticity/ neuroprotection	PDE-4 inhibitor	Prolongs cAMP activity and improves neuronal plasticity (DMT)	Active, not recruiting (NCT03817684)	Tetra Discovery Partners	Apr 2019	Feb 2020
Candesartan	Vasculature	Angiotensin receptor blocker	Improve cerebrovascular functioning (DMT)	Recruiting (NCT02646982)	Emory University	Jun 2016	Sep 2021
Cilostazol	Synaptic plasticity/ neuroprotection	PDE-3 inhibitor	Improve cerebral circulation; reduce accumulation of amyloid and tau phosphorylation (DMT)	Recruiting (NCT02491268)	National cerebral and cardiovascular center, Japan	May 2015	Dec 2020
Crenezumab	Amyloid	Monoclonal antibody targeting soluble oligomers	Remove amyloid (DMT)	Active, not recruiting (NCT01998841)	Genentech, NIA Banner Alzheimer's Institute	Dec 2013	Feb 2022
CT1812	Synaptic plasticity/ neuroprotection	Sigma-2 receptor antagonist; competes with oligomeric A $\beta$ binding	Preserve synaptic plasticity and protect against A $\beta$ -induced synaptic toxicity (DMT)	Recruiting (NCT03507790)	Cognition therapeutics	Oct 2018	Jul 2020
				Active, not recruiting <sup>a</sup> (NCT03493282)	Cognition therapeutics	Apr 2018	Mar 2021
Curcumin + aerobic yoga	Inflammation	Herb with antioxidant and anti-inflammatory properties	Decrease inflammation and oxidation-related neurotoxicity (DMT)	Active, not recruiting (NCT01811381)	VA office of research and development	Jan 2014	Mar 2020
DAOI	Neurotransmitter receptors	NMDA receptor modulation	Enhance NMDA activity (cognitive enhancer)	Recruiting (NCT03752463)	Chang Gung Memorial Hospital, Taiwan	May 2015	Dec 2019
Dapagliflozin	Metabolism and bioenergetics	SGLT2 inhibitor	Improve insulin sensitivity and CNS glucose metabolism (DMT)	Recruiting <sup>a</sup> (NCT03801442)	University of Kansas	Jan 2019	Oct 2020
Daratumumab	Inflammation/ Immunity	Monoclonal antibody targeting CD38	Immunomodulatory effects; regulates microglial activity (DMT)	Recruiting (NCT04070378)	Janssen, Northwell health	Nov 2019	Jun 2022

(Continues)

**TABLE 2** (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
Dasatinib + Quercetin	Inflammation/Immunity	Tyrosine kinase inhibitor (dasatinib); flavonoid (quercetin)	Senolytic therapy approach to reduce senescent cells and tau aggregation (DMT)	Not yet recruiting (NCT04063124)	The University of Texas Health Science Center at San Antonio, Mayo Clinic	Mar 2020	Dec 2022
Deferiprone	Synaptic plasticity/neuroprotection	Iron chelating agent	Reduce reactive oxygen species that damage neurons (DMT)	Recruiting (NCT03234686)	Neuroscience trials Australia	Jan 2018	Dec 2021
Dronabinol	Neurotransmitter Receptors	CB1 and CB2 endocannabinoid receptor partial agonist	Improve neuropsychiatric symptoms (agitation)	Recruiting (NCT02792257)	McLean Hospital, Johns Hopkins University	Mar 2017	Dec 2020
Elderberry Juice	Inflammation	Antioxidant rich in anthocyanins	Improve mitochondrial function (DMT)	Recruiting (NCT02414607)	University of Missouri	Sep 2016	Apr 2020
GB301	Inflammation/Immunity	Regulatory T cells	Promote immune cell homeostasis and reduce neuroinflammation (DMT)	Not yet recruiting <sup>a</sup> (NCT03865017)	GMP BIO, BHT Lifescience Australia	Dec 2019	Dec 2021
Grapeseed Extract	Amyloid	Polyphenolic compound; antioxidant	Anti-oligomerization agent; prevents aggregation of amyloid and tau (DMT)	Recruiting (NCT02033941)	Mount Sinai School of Medicine, NCCIH	Nov 2014	Sep 2020
GRF6019	Synaptic plasticity/neuroprotection, Inflammation	Blood plasma protein fractions from young adult donors	Young blood parabiosis can counteract inflammatory and age-related degeneration in the brain (DMT)	Active, not recruiting (NCT03765762)	Alkahest	Jan 2019	Mar 2020
GV1001	Epigenetic	hTERT peptide vaccine	Mimics the extra-telomeric functions of hTERT to inhibit neurotoxicity, apoptosis, and the production of reactive oxygen species induced by A $\beta$ (DMT)	Not yet recruiting (NCT03959553)	GemVax & Kael	Sep 2019	Feb 2022
Insulin glulisine intranasal	Metabolism and bioenergetics	Increase insulin signaling in the brain	Enhance cell signaling and growth; promote neuronal metabolism (DMT)	Active, not recruiting (NCT02503501)	HealthPartners Institute	Aug 2015	Feb 2020

(Continues)

**TABLE 2** (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
IONIS MAPTRx (BIIB080)	Epigenetic, Tau	Antisense oligonucleotide targeting tau expression; MAPT RNA inhibitor	Reduce tau production (DMT)	Active, not recruiting <sup>a</sup> (NCT03186989)	Ionis pharmaceuticals	Jun 2017	May 2022
Lemborexant (E2006)	Neurotransmitter receptors	Dual antagonist of orexin OX1 and OX2 receptors	Improve neuropsychiatric symptoms (sleep-wake disorders)	Active, not recruiting (NCT03001557)	Eisai, purdue pharma	Dec 2016	Apr 2020
Lenalidomide	Inflammation/Immunity	Anti-neoplastic; immunomodulator	Reduce inflammatory cytokines (TNF- $\alpha$ , IL-6, IL-8); modulate both innate and adaptive immune responses (DMT)	Not yet recruiting (NCT04032626)	Cleveland Clinic, NIA	Feb 2020	Sep 2024
Levetiracetam	Synaptic plasticity/neuroprotection	SV2A modulator	Improve synaptic function; reduce amyloid-induced neuronal hyperactivity (DMT)	Recruiting (NCT02002819)	University of California, San Francisco	Jun 2014	Aug 2020
				Recruiting (NCT03489044)	UCB Pharma, University of Oxford, NHS Foundation Trust	Nov 2018	Jan 2020
				Recruiting (NCT03461861)	Medical College of Wisconsin, NIA	Apr 2019	Mar 2020
				Recruiting (NCT03875638)	Beth Israel Deaconess Medical Center	Aug 2019	Nov 2023
Liraglutide	Metabolism and bioenergetics	Glucagon-like peptide 1 receptor agonist	Improve CNS glucose metabolism (DMT)	Active, not recruiting (NCT01843075)	Imperial College London	Jan 2014	Dec 2019
Lithium	Neurotransmitter receptors	Ion channel modulator	Improve neuropsychiatric symptoms (agitation, aggression, psychosis)	Recruiting (NCT02129348)	New York State Psychiatric Institute, NIA	Jun 2014	Jan 2020

(Continues)



**TABLE 2** (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
LM11A-31-BHS	Synaptic plasticity/ neuroprotection, cell Death	Non-peptide ligand of the p75 neurotrophin receptor (p75NTR)	Inhibits apoptosis signaling and reduces cell death; reduces A $\beta$ -induced synaptic impairment (DMT)	Recruiting <sup>a</sup> (NCT03069014)	Pharmatrophix, (NIA)	Feb 2017	Oct 2019
L-Serine	Inflammation	Naturally occurring dietary amino acid	Reduces brain inflammation and preserves nerve cells (DMT)	Recruiting (NCT03062449)	Dartmouth- Hitchcock Medical Center	Mar 2017	Dec 2020
Lupron (leuprolide acetate depot)	Growth factors and hormones	GnRH receptor agonist	Reduces negative effects of elevated GnRH and gonadotropins on the brain (DMT)	Not yet recruiting (NCT03649724)	New York University	Feb 2020	Feb 2026
LY3002813 (donanemab)	Amyloid	Monoclonal antibody specific for pyroglutamic peptide fragment	Remove amyloid (DMT)	Recruiting (NCT03367403)	Eli Lilly	Dec 2017	Nov 2021
LY3303560 (zaganemab)	Tau	Monoclonal antibody	Remove tau and reduce tau propagation (DMT)	Active, not recruiting (NCT03518073)	Eli Lilly	Apr 2018	Oct 2021
Metabolic cofactor sup- plementation	Metabolism and bioenergetics	Mixture of N- acetylcysteine, L-carnitine tartrate, nicotinamide roboside, and serine	Enhance hepatic-B oxidation and increase mitochondrial activity (cognitive enhancer)	Recruiting (NCT04044131)	Istanbul Medipol University Hospital, ScandiBio Therapeutics	Dec 2019	Sep 2020
Montelukast	Inflammation	Leukotriene receptor antagonist	Reduce inflammatory pathways and neuronal injury (cognitive enhancer)	Recruiting (NCT03402503)- buccal film	IntelGenx Corp.	Nov 2018	Jul 2021
				Recruiting (NCT03991988)- tablet	Emory University	Sep 2019	Aug 2021
Neflamapimod (VX-745)	Synaptic plastic- ity/neuroprotection	p38 MAPK- $\alpha$ inhibitor	Enhances endolysosomal function to reduce synaptic dysfunction (DMT)	Recruiting (NCT03435861)	EIP Pharma	Oct 2018	Jan 2021

(Continues)

**TABLE 2** (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
Nicotinamide	Epigenetic, Tau	Histone deacetylase (HDAC) inhibitor; microtubule protein modulator	Reduce tau-induced microtubule depolymerization and tau phosphorylation (DMT)	Recruiting (NCT03061474)	University of California, Irvine	Jul 2017	Jun 2020
Nicotine transdermal patch	Neurotransmitter receptors	Nicotinic acetylcholine receptor agonist	Enhance acetylcholine signaling (cognitive enhancer)	Recruiting (NCT02720445)	University of Southern California, NIA, ATRI, Vanderbilt University	Jan 2017	Dec 2020
Nilotinib	Proteostasis/proteinopathies	Tyrosine kinase inhibitor; Abl inhibition	Autophagy enhancer; promotes clearance of amyloid and tau proteins (DMT)	Active, not recruiting (NCT02947893)	Georgetown University	Jan 2017	Feb 2020
Omega-3 PUFA	Vasculature	Fish oil concentrate standardized to long chain in n-3 PUFA content	Reduces inflammation and glial activation; enhances amyloid removal (DMT)	Active, not recruiting (NCT01953705)	Oregon Health and Science University, NIA	May 2014	Aug 2019
ORY-2001 (vafidemstat)	Epigenetic	HDAC demethylase (LSD1) inhibitor and MAO-B inhibitor	Targets two enzymes: LSD1, which downregulates HDAC demethylase, and MAO-B, which has neuroprotective properties (DMT)	Recruiting (NCT03867253)	Oryzon genomics, ADDF	May 2019	Nov 2020
Posiphen	Proteostasis/Proteinopathies	Selective inhibitor of APP to reduce amyloid; reduces synthesis of tau and $\alpha$ -synuclein proteins	Reduce amyloid, tau and $\alpha$ -synuclein production (DMT)	Recruiting <sup>a</sup> (NCT029	QR Pharma, ADCS	Mar 2017	Dec 2020
Prazosin	Neurotransmitter receptors	Alpha-1 adrenoreceptor antagonist	Improve neuropsychiatric symptoms (agitation)	Recruiting (NCT03710642)	ADCS, NIA	Jul 2019	Dec 2022

(Continues)

**TABLE 2** (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
PTI-125	Amyloid	Filamin A protein inhibitor	Stabilize the interaction of soluble amyloid and the $\alpha 7$ nicotinic acetylcholine receptor, reducing tau hyperphosphorylation and synaptic dysfunction (DMT)	Recruiting (NCT04079803)	Cassava Sciences, NIA	Aug 2019	Apr 2020
PQ912	Amyloid	Glutamyl cyclase (QC) enzyme inhibitor	Reduce pyroglutamate $A\beta$ (pGlu- $A\beta$ ) production and amyloid plaques (DMT)	Not yet recruiting (NCT03919162)	Probiodrug, ADCS, NIA	Jan 2020	Apr 2023
Riluzole	Synaptic Plasticity/ Neuroprotection	Glutamate receptor antagonist	Reduce glutamate-mediated excitotoxicity (DMT)	Active, not recruiting (NCT01703117)	Rockefeller University	Nov 2013	Sep 2020
Rifaximin	Inflammation/ Infection/ Immunity	Antibiotic	Reduce pro-inflammatory cytokines secreted by harmful gut bacteria (DMT)	Recruiting (NCT03856359)	Duke University, Bausch Health	Apr 2019	Feb 2021
RPh201	Synaptic plasticity/neuroprotection	Undisclosed; extract from a botanical source	Neuroprotective from amyloid and vascular-related neuropathology (DMT)	Recruiting (NCT03462121)	Regenera pharma	Mar 2018	Jun 2020
Sargramostim (GM-CSF)	Inflammation/Immur	Granulocyte macrophage colony stimulating factor	Immune system stimulator that removes amyloid and improves synaptic function (DMT)	Active, not recruiting (NCT01409915)	University of Colorado, Denver, The Dana Foundation	Mar 2011	May 2020
Semorinemab (RO7105705)	Tau	Monoclonal antibody	Remove extracellular tau (DMT)	Active, not recruiting (NCT03289143)	Genentech	Oct 2017	Sep 2022
				Recruiting (NCT03828747)	Genentech	Jan 2019	Jun 2023
S-equol (AUS-131)	Metabolism and bioenergetics	Agonist of non-hormonal estrogen receptor B located on mitochondria	Mitochondrial function potentiation; improve synaptic functioning and neuronal survival (DMT)	Recruiting (NCT03101085)	Ausio pharmaceuticals	May 2017	Jun 2020

(Continues)

**TABLE 2** (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
<b>T3D-959</b>	Metabolism and bioenergetics	Dual agonist of PPAR- $\delta$ and PPAR- $\gamma$	Regulate glucose and lipid metabolism; reduce insulin resistance (DMT)	Recruiting (NCT04251182)	T3D therapeutics, NIA	Feb 2020	Aug 2021
<b>T-817MA</b> (edonerpic)	Synaptic Plasticity/ Neuroprotection	Activates sigma receptors	Promotes neurite outgrowth, preserves synaptic plasticity; protects against amyloid toxicity (DMT)	Recruiting (NCT04191486)	Toyama Chemical	Dec 2019	Oct 2022
<b>Tacrolimus</b>	Synaptic plasticity/neuroprotection	Calcineurin inhibitor	Prevents amyloid-induced dendritic spine loss and synaptic dysfunction (DMT)	Not yet recruiting (NCT04263519)	Massachusetts General Hospital	Mar 2020	Dec 2021
<b>Telmisartan &amp; Perindopril</b>	Vasculature	Angiotensin II receptor blocker (telmisartan); angiotensin converting enzyme inhibitor (perindopril)	Improve vascular functioning (DMT)	Recruiting (NCT02085265)	Sunnybrook Health Sciences Centre, ADDF	Mar 2014	Mar 2021
<b>Thiethylperazine (TEP)</b>	Amyloid	Activates transport protein ABCC1	Remove amyloid (DMT)	Active, not recruiting (NCT03417986)	Immugenetics AG	Nov 2017	Jul 2021
<b>Valacyclovir</b>	Infection/ Immunity	Antiviral against HSV-1 and -2 infection	Prevents amyloid aggregation and plaque deposition (DMT)	Recruiting (NCT02997982)	Umea University	Dec 2016	Apr 2020
				Recruiting (NCT03282916)	New York State Psychiatric Institute, NIH, NIA	Feb 2018	Aug 2022
<b>VGH-AD1</b>	Undisclosed	Traditional Chinese herbal medicine	Undisclosed (cognitive enhancer)	Not yet recruiting (NCT04249869) <sup>a</sup>	Taipei Veterans General Hospital, Taiwan	Feb 2020	Dec 2020

Abbreviations: A $\beta$ , amyloid beta; ABCC1, ATP binding cassette subfamily C member 1; ADCS, Alzheimer's Disease Cooperative Study; ADDF, Alzheimer's Drug Discovery Foundation; APP, amyloid precursor protein; ATRI, Alzheimer's Therapeutic Research Institute; CADRO, Common Alzheimer's Disease and Related Disorders Research Ontology; cAMP, cycling adenosine monophosphate; CB, cannabinoid; DMT, disease-modifying therapy; GM-CSF, granulocyte-macrophage colony-stimulating factor; GnRH, gonadotropin-releasing hormone; HSV, herpes simplex virus; hTERT, human telomerase reverse transcriptase; HT, hydroxytryptamine; MAPK, mitogen-activated protein kinase; NCCIH, National Center for Complementary and Integrative Health; NIA, National Institute on Aging; NMDA, N-methyl-D-aspartate; PDE, phosphodiesterase; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acids; SGLT2, sodium glucose transporter 2; SV2A, synaptic vesicle protein 2A.

Note: Sixty-five agents in 73 Phase 2 clinical trials currently ongoing as of February 27, 2020 according to ClinicalTrials.gov.

Note: Bolded terms represent new agents into the 2020 Phase 2 pipeline since 2019.

Note: The following agents have been identified as completed/terminated per company press releases and have been removed from the current pipeline although they are still listed as ongoing on ClinicalTrials.gov: elenbecostat (NCT02322021), NA-831 (NCT03538522).

<sup>a</sup>Phase 1/2 trials.

**TABLE 3** Agents in Phase 1 of Alzheimer's disease drug development (ClinicalTrials.gov accessed February 27, 2020)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
AAV-hTERT	Epigenetic	hTERT delivered via transduction using AAV	Extending telomeres may benefit AD; reduce amyloid-induced neurotoxicity; effects on multiple cellular pathways (DMT)	Recruiting (NCT04133454)	Libella gene therapeutics	Oct 2019	Jan 2021
AAVrh.10hAPOE2	Epigenetic	Serotype rh. 10 AAV gene transfer vector expressing the cDNA coding for ApoE2	Conversion of the ApoE protein isoforms in the CSF of ApoE4 homozygotes from ApoE4 to ApoE2-ApoE4 (DMT)	Recruiting (NCT03634007)	Cornell University	Oct 2019	Dec 2021
AL002	Inflammation	Monoclonal antibody targeting TREM2 receptors	Promote microglial clearance of amyloid and other toxic proteins (DMT)	Recruiting (NCT03635047)	Alector	Nov 2018	Mar 2020
AL003	Inflammation	Monoclonal antibody targeting SIGLEC-3 (CD33)	Reactivates microglia and immune cells in the brain; improve microglial clearance of toxic proteins (DMT)	Recruiting (NCT03822208)	Alector	Mar 2019	Jul 2020
Allopregnanolone (Allo)	Growth factors/hormones	GABA-A receptor modulator; neurosteroid	Promote neurogenesis; reduce inflammation (DMT)	Recruiting (NCT03748303)	University of Southern California, University of Arizona, Alzheimer's Association	Oct 2019	Oct 2020
anle138b	Tau	Aggregation inhibitor	Prevents/reduces aggregation of tau, $\alpha$ -synuclein and prion proteins (DMT)	Recruiting (NCT04208152)	MODAG, quotient sciences	Dec 2019	Oct 2020
BDPP (bioactive dietary polyphenol preparation)	Metabolism and bioenergetics, amyloid	Combination of grape seed polyphenolic extract and resveratrol	Prevents amyloid and tau aggregation (DMT)	Recruiting (NCT02502253)	Johns Hopkins University, Mount Sinai School of Medicine	Jun 2015	Jun 2020
BIB076	Tau	Monoclonal antibody	Remove tau and reduce tau propagation (DMT)	Active, not recruiting (NCT03056729)	Biogen	Feb 2017	Mar 2020

(Continues)

**TABLE 3** (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
CT1812	Synaptic plasticity/neuroprotectivity	Sigma-2 receptor antagonist; competes with oligomeric A $\beta$ binding	Preserve synaptic plasticity and protect against A $\beta$ -induced synaptic toxicity (DMT)	Recruiting (NCT03522129)	Cognition therapeutics	May 2018	Mar 2021
Dabigatran	Metabolism and bioenergetics, vasculature	Direct thrombin inhibitor	Reduce neurovascular damage (DMT)	Not yet recruiting (NCT03752294)	University of Rhode Island, ADDF, boehringer ingelheim	Nov 2018	Dec 2021
Efavirenz	Metabolism and bioenergetics, vasculature	Antiretroviral; non-nucleoside reverse transcriptase inhibitor	Promote cholesterol removal from the brain and enhance amyloid reduction (DMT)	Recruiting (NCT03706885)	Case Western Reserve University, Cleveland Medical Center, Massachusetts General Hospital	May 2018	Dec 2020
Empagliflozin	Metabolism and bioenergetics	SGLT2 inhibitor	Improve glycemic control and enhance neuronal function (DMT)	Recruiting (NCT03852901)	NIA	Mar 2019	Dec 2022
Escitalopram and Venlafaxine	Neurotransmitter receptors	SSRI (escitalopram), SNRI (venlafaxine)	Improve neurotransmission (cognitive enhancer)	Recruiting (NCT03274817)	New York University	Jul 2017	Jan 2020
Fecal microbiota transplant (FMT)	Inflammation	Oral FMT intervention	Improve gut microbiota; reduce AD pathology (DMT)	Recruiting (NCT03998423)	University of Wisconsin, Madison	Nov 2019	May 2022
J147	Metabolism and bioenergetics	Mitochondrial ATP synthase inhibitor	Increases use of free fatty acid to increase ketones for energy use; vascular protective effects (DMT)	Recruiting (NCT03838185)	Abrexa	Jan 2019	Jan 2020
JNJ-40346527	Inflammation	CSF-1R antagonist	Attenuates microglial proliferation and neurodegeneration (DMT)	Not yet recruiting (NCT04121208)	Janssen, University of Oxford	Nov 2019	Nov 2021
Lu AF87908	Tau	Monoclonal antibody	Remove tau (DMT)	Recruiting (NCT04149860)	Lundbeck	Sep 2019	Mar 2021
MK-4334	Growth Factors and Hormones	Corticosteroid	Reduce inflammation (DMT)	Not yet recruiting (NCT03740178)	Merck	Sep 2019	Feb 2020

(Continues)



**TABLE 3** (Continued)

Agent	CADRO mechanism class	Mechanism of action	Therapeutic purpose	Status(CT.gov ID)	Sponsor	Start date	Estimated end date
<b>NNI-362</b>	Neurogenesis	Nerve cell proliferation	Enhance neurogenesis; activates progenitor cells (DMT)	Recruiting (NCT04074837)	Neuronascent, NIA	Aug 2019	Apr 2020
<b>RO7126209</b>	Amyloid	Monoclonal antibody; "brain-shuttle" gantenerumab	Remove amyloid (DMT)	Recruiting (NCT04023994)	Roche	Aug 2019	Jul 2020
Salsalate	Inflammation	Non-steroidal anti-inflammatory	Reduce inflammation and neuronal injury (DMT)	Recruiting (NCT03277573)	University of California, San Francisco	Jul 2017	Oct 2019
Telmisartan	Vasculature	Angiotensin II receptor blocker	Improve vascular function with effects on amyloid pathology (DMT)	Recruiting (NCT02471833)	Emory University	Apr 2015	Jun 2020
<b>TPI-287</b>	Tau	Tubulin-binding and microtubule-stabilization	Reduce tau-mediated cellular damage (DMT)	Active, not recruiting (NCT01966666)	University of California, San Francisco	Nov 2013	Nov 2019
<b>Tricaprilin (AC-DS-03)</b>	Metabolism and bioenergetics	Caprylic triglyceride; ketone body stimulant	Induce ketosis to improve mitochondrial metabolism (DMT)	Recruiting (NCT03971123)	Cerecin	Aug 2019	Aug 2020
				Not yet recruiting (NCT04268953)	Cerecin	Feb 2020	Jul 2020
<b>Vorinostat</b>	Epigenetic	Histone deacetylase (HDAC) inhibitor	Neuroprotection and enhanced synaptic plasticity (DMT)	Recruiting (NCT03056495)	German Center for Neurodegenerative Diseases, University Hospital, Bonn, University of Gottingen	Sep 2017	Mar 2022
<b>XPro1595</b>	Inflammation	TNF inhibitor	Reduce neuroinflammation	Recruiting (NCT03943264)	Immune bio, Alzheimer's association	Nov 2019	Dec 2020

Abbreviations: AAV, adeno-associated virus; A $\beta$ , amyloid beta; ADDF, Alzheimer's Drug Discovery Foundation; ApoE, apolipoprotein E; CADRO, Common Alzheimer's Disease and Related Disorders Research Ontology; CSF, cerebrospinal fluid; CSF-1R, colony-stimulating factor 1 receptor; DMT, disease-modifying therapy; GABA, gamma-aminobutyric acid; hTERT, human telomerase reverse transcriptase; NIA, National Institute on Aging; RIPK1, receptor-interacting serine/threonine-protein kinase 1; SGLT2, sodium glucose co-transporter 2; SIGLEC-3, sialic acid-binding Ig-like lectin 3; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TREM2, triggering receptor expressed on myeloid cells 2.

Note: Twenty-seven agents in 27 Phase 1 clinical trials currently ongoing as of February 27, 2020 according to ClinicalTrials.gov.

Note: Bolded terms represent new agents into the 2020 Phase 1 pipeline since 2019.

academic medical centers (with funding from NIH, industry, and/or other entities), and 6 trials (11%) are by other entities. Figure 4 shows the sponsor of repurposed agents compared to non-repurposed agents in Phase 2 and Phase 3 trials of the AD pipeline.

### 3.6 | Trial locations

Clinical trials require many sites to participate in trials to recruit a sufficient number of participants in a short enough period of time to make

**TABLE 4** Stem cell therapy in clinical trials for Alzheimer's disease (ClinicalTrials.gov accessed February 27, 2020)

Agent	Phase	Status(CT.gov ID)	Sponsor	Subject characteristics	Amyloid evidence at entry
Allogeneic human MSCs	1	Recruiting (NCT04040348)	University of Miami	Mild to moderate AD with MMSE of 20-26	Amyloid PET
Allogeneic human MSCs	1	Active, not recruiting (NCT02600130)	Longeveron	Mild to moderate AD with MMSE of 18-24	Amyloid PET
Autologous adipose-derived MSCs	1/2	Active, not recruiting (NCT04228666)	Hope biosciences	Preclinical/MCI	Amyloid PET
Human umbilical cord blood-derived MSCs (NEUROSTEM)	1/2	Recruiting (NCT02054208)	Medipost	Probable AD with KMMSE of 18-26	Amyloid PET
	1/2	Recruiting, extension study (NCT03172117)	Medipost	Probable AD with KMMSE of 18-26	Amyloid PET
Human umbilical cord blood-derived MSCs	1/2	Ongoing (NCT02672306)	South China research center, Sun Yat-Sen University	Probable AD with MMSE of 10-26	Not required
Allogeneic human MSCs	2	Recruiting (NCT02833792)	Stemedica	Mild to moderate AD with MMSE of 12-24	Amyloid PET

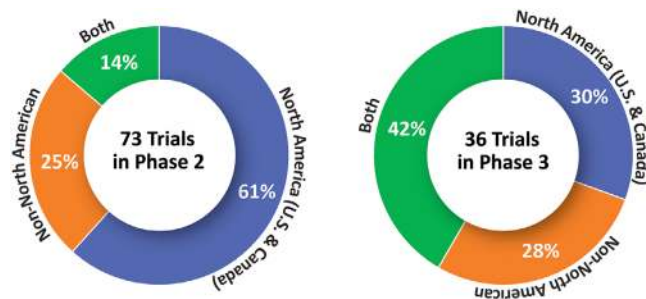
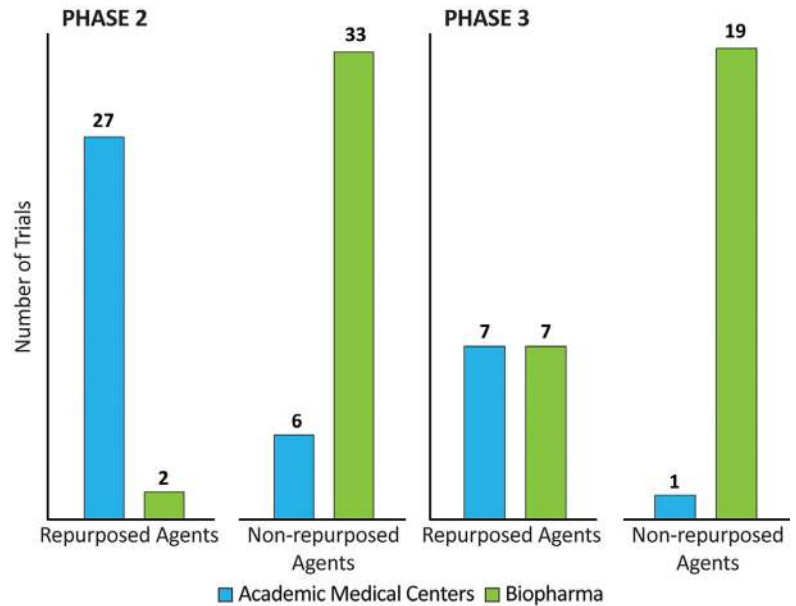
Abbreviations: AD, Alzheimer's disease; KMMSE, Korea Mini-Mental State Examination; MMSE, Mini-Mental State Examination; MSC, mesenchymal stem cell; PET, positron emission tomography.

**TABLE 5** Trial sponsor for each phase of Alzheimer's disease drug development (ClinicalTrials.gov accessed February 27, 2020)

Sponsor	N of trials (%)			
	Phase 1	Phase 2	Phase 3	Total
Biopharma industry	12 (44%)	28 (38%)	22 (61%)	62 (46%)
Academic medical centers	12 (44%)	33 (45%)	8 (22%)	53 (39%)
NIH	1 (4%)	0	0	1 (1%)
Other federal agencies (eg, VA)	0	3 (4%)	1 (3%)	4 (3%)
Industry and NIH	1 (4%)	3 (4%)	1 (3%)	5 (4%)
Industry and consortium/foundation	1 (4%)	3 (4%)	2 (6%)	6 (4%)
NIH and consortium/foundation	0	1 (1%)	0	1 (1%)
NIH and consortium/foundation and industry	0	2 (3%)	1 (3%)	3 (2%)
NIH and consortium/foundation and industry and academic	0	0	1 (3%)	1 (3%)

Abbreviations: NIH, National Institutes of Health; VA, veterans affairs.

**FIGURE 4** Trial sponsor for repurposed versus non-repurposed agents in the Alzheimer's disease pipeline (ClinicalTrials.gov accessed February 27, 2020) (Figure by Mike de la Flor)



**FIGURE 5** Location of sites for Phase 2 and Phase 3 trials in the Alzheimer's disease drug development pipeline (ClinicalTrials.gov accessed February 27, 2020) (Figure by Mike de la Flor)

the trial feasible.<sup>20</sup> Figure 5 shows that 30% of Phase 3 and 61% of Phase 2 trials include sites only in North America; 28% of Phase 3 and 25% of Phase 2 trials involve only non-North American clinical trial sites; and 42% of Phase 3 and 14% of Phase 2 trials include sites in both North America and non-North American countries.

### 3.7 | Clinical trial recruitment

When considering the total number of sites involved in Phase 3 DMT trials, the total number of participants to be recruited, and the average number of months allowed for recruitment, the calculated average productivity of sites is 0.19 participants/site/month. In trials of symptomatic agents in Phase 3, the calculated average productivity of sites is 0.25 participants/site/month. Some types of trials are more difficult to enroll: Phase 3 prevention trials involving asymptomatic at-risk individuals treated with disease-modifying agents recruit at a rate of 0.26 participants/site/month; prodromal/mild AD trials recruit at a rate of 0.16 participants/site/month; and mild-to-moderate AD dementia trials have a rate of 0.29 participants/site/month. The total number of

participants required for all currently recruiting trials is 31,314 participants.

### 3.8 | Trial completion date

Thirty-six trials are listed as "completed" on ClinicalTrials.gov since our last report in 2019. The actual completion date of a trial is typically much later than the anticipated completion date at trial initiation. The mean difference between the actual completion date and the anticipated completion date was 30 weeks for completed trials in Phase 1, 32 weeks for Phase 2, and 72 weeks for Phase 3, respectively.

### 3.9 | Biomarkers

Table 6 shows the biomarkers used as outcome measures in current Phase 2 and Phase 3 AD clinical trials of DMTs as described in the federal website; not all trial descriptions in ClinicalTrials.gov note if biomarkers are included in the trial.

AD biomarkers served as secondary outcome measures in 14 Phase 3 trials of DMTs and 27 Phase 2 trials of DMTs. The most common biomarkers used were cerebrospinal fluid (CSF) amyloid, CSF tau, volumetric magnetic resonance imaging (MRI), and amyloid positron emission tomography (PET). Tau imaging is increasingly involved in AD drug development programs and was included as a secondary outcome in three (14%) Phase 3 and four (7%) Phase 2 trials of DMTs. Of the 21 Phase 3 DMT trials, 5 (24%) used amyloid PET as an entry criterion, 2 (10%) used CSF-amyloid, and 4 (19%) used either amyloid PET or CSF-amyloid. Nine (15%) of 61 Phase 2 DMT trials used amyloid PET as an entry criterion, nine (15%) used CSF-amyloid, and nine (15%) used either amyloid PET or CSF-amyloid. Ten (47%) DMT trials in Phase 3 and 34 (55%) in Phase 2 did not require biomarker confirmation of AD for trial entry.

**TABLE 6** Biomarkers as outcome measures in Phase 2 and Phase 3 disease-modifying therapies trials (ClinicalTrials.gov accessed February 27, 2020)

Biomarker	N of trials (%)	
	Phase 2	Phase 3
CSF amyloid	15 (25%)	10 (48%)
CSF tau	17 (28%)	9 (43%)
FDG-PET	7 (11%)	1 (5%)
Vmri	8 (13%)	8 (38%)
Plasma amyloid	7 (11%)	2 (10%)
Plasma tau	2 (3%)	1 (5%)
Amyloid PET	5 (8%)	7 (33%)
Tau PET	4 (7%)	3 (14%)

Abbreviations: CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; PET, positron emission tomography; vMRI, volumetric magnetic resonance imaging.

### 3.10 | Trial entry criteria and primary outcomes

The initiation of prevention trials in preclinical patients and treatment trials of patients with very early symptoms of AD has led to new trial population definitions and novel outcome measures (Table 7). Entry criteria and outcomes must be appropriate to identify the population of interest. As shown in Table 7, trials with similar descriptions of the population (eg, prodromal AD/mild AD dementia) have slightly different Mini-Mental State Examination (MMSE) criteria for entry into the study, creating slightly different cohorts and possibly different disease trajectories. The Clinical Dementia Rating–sum of boxes (CDR-sb) is the most widely used outcome for trials of prodromal or prodromal/mild disease, but some trials have dual outcomes traditionally used in AD dementia trials. There is substantial heterogeneity among the instruments used as primary outcomes in prevention trials although the elements of the tools overlap.

### 3.11 | Longitudinal observations

Figure 6 shows the pipeline activity over the past 5 years by CADRO category. Amyloid and tau mechanisms are further divided into small molecule therapies and monoclonal antibodies. There is a trend for increasing diversification of the pipeline with a greater number of tau-targeted, anti-inflammatory, synaptic and neuroprotective, metabolic, neurogenesis, and epigenetic agents over the 5 years of observation.

## 4 | DISCUSSION

The U.S. FDA approved 53 new novel therapies in 2019, including 48 new molecular entities and 3 therapies and 2 vaccines representing biological products.<sup>21</sup> Twelve agents for neurological disorders were

among the 48 approved therapies. There were three sleep disorder treatments; three drugs for psychiatric conditions; two anti-migraine therapies; two drugs for childhood neuromuscular disorders; and one treatment each for partial onset seizures, Parkinson's disease with excessive "off" episodes, and relapsing multiple sclerosis. The two neuromuscular disorder therapies and the agent for relapsing multiple sclerosis can be regarded as DMTs. The approved diagnostic tests included 18-F fluorodopa PET for the diagnosis of parkinsonian disorders. There were no treatments approved in the United States for AD and no DMTs for any primary neurodegenerative disorder.

GV-971 (Oligomannate) became the first drug approved for treatment of AD since 2003.<sup>22-24</sup> The agent was approved in China for improvement of cognition in patients with mild-to-moderate AD dementia not treated with cholinesterase inhibitors or memantine based on a Phase 3 clinical trial that demonstrated a significant drug-placebo difference on the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) and a trend toward a difference on the Clinician Interview-Based Impression of Change with caregiver input (CIBIC-plus). These outcomes satisfied the requirements of the National Medical Products Administration (NMPA; Chinese equivalent of the FDA) for approval as an AD therapy. Non-clinical studies suggest that GV-971 has an effect on the dysbiosis of the gut microbiome to decrease secreted amino acids (phenylalanine and isoleucine) that stimulate proliferation of peripheral pro-inflammatory T-helper cells and cross the blood-brain barrier and contribute to neuroinflammation.<sup>25</sup>

Aducanumab is a monoclonal antibody developed to remove fibrillar amyloid beta (A $\beta$ ) as a means of ameliorating progression of cognitive impairment in AD. The agent had a successful Phase 1B trial demonstrating a dose- and time-dependency for A $\beta$  reduction with a beneficial impact on some clinical measures after 12 months of treatment.<sup>26</sup> Two large Phase 3 clinical trials were initiated to confirm the clinical and biological effects. A planned futility analysis concluded that continuing the trials was futile and both were stopped. Further analyses that included participants exposed for longer periods of time at higher antibody doses indicated that aducanumab reduced brain amyloid and decreased the rate of decline on the CDR-sb, the pre-specified primary outcome. On the basis of these analyses, the sponsor has initiated discussions with the FDA regarding marketing approval for aducanumab.<sup>27</sup>

BAN2401, a monoclonal antibody targeting prefibrillar amyloid,<sup>28</sup> completed a Phase 2 trial in 2018 with evidence of amyloid reduction and slowing of cognitive decline.<sup>29</sup> This agent has now entered Phase 3. Crenezumab, a monoclonal antibody targeting oligomers, had a Phase 2 trial suggesting efficacy in participants with mild AD,<sup>30,31</sup> a Phase 3 program was recently halted due to futility. Crenezumab is being assessed in a prevention trial involving a Colombian kindred with autosomal dominant AD.<sup>32</sup> Gantenerumab is being assessed in Phase 3 trials after a trial in prodromal disease stopped for futility suggested that higher doses might be efficacious.<sup>33</sup> Gantenerumab and solanezumab failed to show drug-placebo differences in clinical outcomes of the Dominantly Inherited Alzheimer Disease–Treatment Unit (DIAN-TU) study of individuals with autosomal dominant AD. Biomarker studies

**TABLE 7** Trial entry criteria and primary outcome measures for Phase 2/3 and 3 disease-modifying therapies trials (ClinicalTrials.gov accessed February 27, 2020)

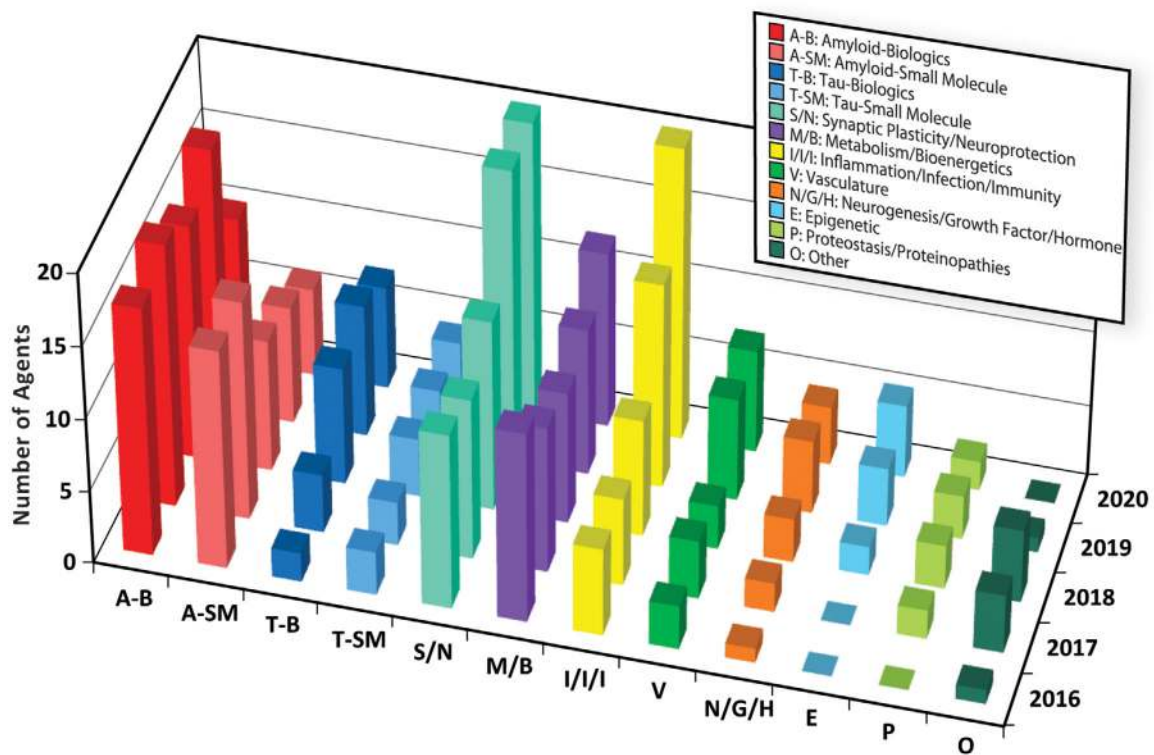
Agent	Sponsor	CT.gov ID	Trial name	Subject population	MMSE	Primary outcome assessment tool
Aducanumab	Biogen	NCT04241068	EMBARK	MCI due to AD or mild AD	–	Safety
AGB101	AgeneBio, NIA	NCT03486938	HOPE4MCI	MCI due to AD	24–30	CDR-SB
ALZT-OP1	AZTherapies	NCT02547818	COGNITE	Early AD	–	CDR-SB
ANAVEX2-73 (blarcamesine)	Anavex Life Sciences	NCT03790709	ANAVEX2-73-AD-004	MCI due to AD or mild AD	20–28	ADAS-Cog, ADCS-ADL
Azeliragon	vTv therapeutics	NCT03980730	Elevage	Mild AD with elevated HbA1c	21–26	ADAS-Cog14, CDR-SB
BAN2401	Eisai, biogen	NCT03887455	Clarity AD	MCI due to AD or mild AD	22–30	CDR-SB
BHV4157 (troriluzole)	Biohaven pharma, ADCS	NCT03605667	T2 Protect	Mild to moderate AD	–	ADAS-Cog11, CDR-SB
CAD106	Novartis, banner Alzheimer's institute, NIA, Alzheimer's association, amgen	NCT02565511	Generation S1	Preclinical; homozygous ApoE4 genotype	≥24	Time to diagnosis of MCI or dementia due to AD, APCC
COR388	Cortexyme	NCT03823404	GAIN	Mild to moderate AD	12–24	ADAS-Cog11, CDR-SB
Gantenerumab	Roche	NCT02051608	Marguerite road	Mild AD	–	ADAS-Cog13, ADCD-ADL
		NCT01224106	SCarlet road	Prodromal AD	≥24	CDR-SB
		NCT03444870	GRADUATE I	Prodromal or mild AD	≥22	CDR-SB
		NCT03443973	GRADUATE II	Prodromal or mild AD	≥22	CDR-SB
Gantenerumab and solanezumab	Washington University, Eli Lilly, Roche, NIA, Alzheimer's Association	NCT01760005	DIAN-TU-001	Carriers of dominantly inherited AD mutations who are cognitively normal or with MCI or mild dementia	–	DIAN-TU cognitive composite score
Icosapent ethyl	VA office of research and development, University of Wisconsin, Madison	NCT02719327	BRAVE-EPA	Cognitively normal with parental history of AD and increased prevalence of ApoE4	–	Brain blood flow using arterial spin-labeling MRI
Losartan and amlodipine and atorvastatin + exercise	University of Texas Southwestern	NCT02913664	rrAD	Preclinical; family history of dementia or subjective cognitive decline with high blood pressure	≥26	ADCS-PACC, NIH-TB Cognition Battery

(Continues)

**TABLE 7** (Continued)

Agent	Sponsor	CT.gov ID	Trial name	Subject population	MMSE	Primary outcome assessment tool
Mastinib	AB Science	NCT01872598	AB09004	Mild to moderate AD	12–25	ADCS-ADL, ADAS-Cog
Metformin	Columbia University, NIA, EMD serono	NCT04098666	MAP	aMCI, overweight or obese	≥24	FCSRT
Solanezumab	Eli Lilly, ATRI	NCT02008357	A4	Preclinical with amyloid evidence	25–30	ADCS-PACC
Tricaprilin	Cerecin	NCT04187547	AC-19-020	Mild to moderate AD who are ApoE4 non-carriers	14–26	ADAS-Cog11
TRx0237	TauRx therapeutics	NCT03446001	LUCIDITY	Probable AD or MCI due to AD	16–27	ADAS-Cog11, ADCS-ADL

Abbreviations: ADAS-Cog, Alzheimer’s Disease Assessment Scale–Cognitive Subscale; ADCS-ADL, Alzheimer’s Disease Cooperative Study–Activities of Daily Living; ADCS-PACC, Alzheimer’s Disease Cooperative Study–Preclinical Alzheimer Cognitive Composite; APCC, Alzheimer’s Prevention Initiative Composite Cognitive; ApoE, apolipoprotein E; ATRI, Alzheimer’s Therapeutic Research Institute; CDR-SB, Clinical Dementia Eating–Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; HbA1c, hemoglobin A1c; MCI, mild cognitive impairment; NIA, National Institute on Aging; NIH-TB, National Institutes of Health toolbox.



**FIGURE 6** Targets of Alzheimer’s disease therapeutics by Common Alzheimer’s Disease and Related Disorders Research Ontology (CADRO) category: 2016–2020 (ClinicalTrials.gov accessed February 27, 2020) (Figure by Mike de la Flor)

showed that gantenerumb decreased brain amyloid and ameliorated the increase of CSF markers of neurodegeneration.

Several tau-targeting monoclonal antibodies are in trials for AD and some are in trials for other tauopathies (ABBV-8E12, BIIB076, BIIB092, Lu AF87908, LY3303560 [zaganemab], RO7105705

[semorinemab]). A trial of ABBV-8E12 in progressive supranuclear palsy (PSP) was recently halted for futility; the antibody remains in trials for AD. A trial of the tau antibody, gosuranemb, in a PSP population, failed to meet its primary endpoints and development of this antibody for tauopathies has been halted.



Several trials of beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitors were stopped for futility or toxicity. Verubecestat trials of mild-to-moderate AD and prodromal AD were discontinued for futility.<sup>34,35</sup> Atabecestat was stopped for hepatotoxicity. Umibecestat (CNP520) was stopped when it was found to cause accelerated cognitive decline. Elenbecestat trials were suspended for an unfavorable harm/benefit ratio. Analyses of data from the verubecestat trial in prodromal AD showed increased cognitive decline and greater atrophy on volumetric MRI in the active treatment group.<sup>35</sup> Retrospective analyses of atabecestat also demonstrated increased cognitive impairment compared to the placebo group. While it is possible that less complete BACE inhibition or use of BACE inhibitors earlier in the course of the AD continuum might define a niche for these agents, the cumulative evidence of cognitive toxicity makes it difficult to design development programs that ensure participant safety.

A 1-year, double-blind, placebo-controlled Phase 2 trial of edonergic maleate (T-817MA)—an agent that in animal models protected against amyloid-induced neurotoxicity, promoted neurite outgrowth, and preserved hippocampal synapses in tau transgenic mice—had no clinical effect in participants with mild to moderate AD.<sup>36</sup> A Phase 2 trial of T-817MA has been initiated to evaluate the drug's effect on CSF-tau in patients with MCI due to AD or mild AD.

Intepirdine and idalopirdine are 5-HT<sub>6</sub> inhibitors that failed to establish efficacy in recent trials and development of these agents was stopped.<sup>37</sup> In both cases, dosing issues remained unresolved by the trials. Masuperdine (SUVN-502), another 5-HT<sub>6</sub> inhibitor, completed a Phase 2 clinical trial in 2019 and was shown not to be efficacious for cognition in patients receiving donepezil and memantine.

Xanamem an 11- $\beta$ -hydroxysteroid receptor inhibitor whose development program was based on the adverse effects of steroids on hippocampal function and the evidence of steroid dysregulation in AD<sup>38</sup> failed in a Phase 2 trial to establish a drug-placebo difference. The negative outcome was similar to that observed with an earlier drug in this class, ABT-854.<sup>39</sup>

Infections and inflammation are targeted by several drugs in the current pipeline. COR388 antagonized gingipain produced by *P. gingivalis* and blocked A $\beta$ <sub>1-42</sub> production, reduced neuroinflammation, and rescued neurons in the hippocampus of mice.<sup>40</sup> Substantial evidence links herpes virus infection to AD and valacyclovir targets this relationship.<sup>41</sup> GV-971 and rifaximin may reduce brain inflammation through effects on the microbiome.<sup>25</sup> These trials are based on theories that infections or inflammation induced in other ways are central to causing or exacerbating AD. The outcomes of the trials will help inform these underlying concepts.

Treatments for neuropsychiatric symptoms of AD had successes in 2019/2020. The Harmony trial of pimavanserin for dementia-related psychosis (DRP) was discontinued early on the basis of a robust drug-placebo difference in patient relapse after withdrawal from drug or placebo in a relapse prevention trial. This trial was unique in including five types of dementia with psychosis—AD, Parkinson's disease dementia, dementia with Lewy bodies, frontotemporal dementia, vascular dementia—and using a randomized withdrawal design to demonstrate drug efficacy.<sup>42</sup> There are several ongoing trials of agitation in AD. A

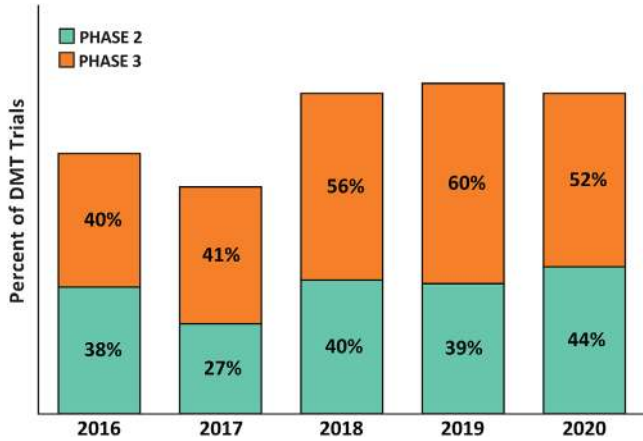
recently reported trial of nabilone (a partial agonist of cannabinoid receptors 1 and 2) showed reduced agitation and improvement on the MMSE but poorer cognition on the Severe Impairment Battery and sedation in association with active treatment compared to placebo.<sup>43</sup> A fixed dose and a flexible dose study of brexpiprazole for agitation in AD demonstrated that in both studies the 2 mg dose produced a significant reduction in agitation while the 1 mg dose did not.<sup>44</sup> A confirmatory trial is in progress. Two trials of dextromethorphan/quinidine that had a positive Phase 2 trial<sup>45</sup> failed to reduce agitation in a Phase 3 program. The selective serotonin reuptake inhibitor (SSRI) citalopram has previously shown to reduce agitation in AD but also prolonged the QT interval. An ongoing study will assess the effects of the S(+)-enantiomer escitalopram using an identical study design.<sup>46,47</sup>

Insomnia in AD, a major challenge for patients and caregivers, was shown to respond to treatment with suvorexant, a dual orexin antagonist, in a randomized clinical trial.<sup>48</sup> The trial demonstrated that participants receiving active therapy had increased time asleep and decreased wakefulness after sleep onset (WASO). The package insert has been modified to include the efficacy findings and the side effects observed in the AD trial.

Proof-of-concept (POC) trials are essential as a means of generating data to inform go/no go decisions for larger trials. Rasagiline, an agent approved for the treatment of motor disturbances in Parkinson's disease, was assessed in a POC trial using fluorodeoxyglucose (FDG) PET as the primary outcome.<sup>49</sup> The pre-specified primary outcome was met, with less decline of metabolism in the group receiving active treatment. Another monoamine oxidase inhibitor—ladostigil—that has neuroprotective effects in cell preparations and animal models was found not to delay the progression from MCI to AD dementia when given in low doses for 3 years.<sup>50</sup>

Repurposed agents are increasingly included in the AD drug development pipeline.<sup>16-18</sup> There are 14 repurposed agents in Phase 3 trials, 28 in Phase 2 trials, and 10 in Phase 1 trials. The difficulty of generating intellectual property protection for repurposed agents makes them less attractive as development candidates for biopharmaceutical companies and, because of their lower costs, more attractive to academic drug developers. Biopharmaceutical companies are sponsors of 44% of Phase 3 repurposing trials and 6% of Phase 2 repurposing trials; this compares to their sponsorship of 95% of non-repurposed Phase 3 and 80% of non-repurposed Phase 2 trials (Figure 4). Repurposed agents represent a larger fraction of the AD drug development compared to 5 years ago: there were 32 repurposed agents in 2016 (33% of the pipeline) compared to 52 repurposed agents in 2020 (43% of the pipeline).

Biomarkers play increasingly important roles in AD drug development.<sup>51</sup> Figure 7 shows the percentage of trials of disease-modifying agents (biologics and small molecules) that required confirmation of the presence of amyloid at baseline over the past 5 years. This reflects the recognition that the amnesic dementia phenotype is a phenocopy without corresponding AD-continuum pathology in 20% to 30% of patients.<sup>52</sup> Demonstration of the presence of AD pathology creates the appropriate population for assessment for agents that require AD-related biological targets for their mechanism of action.



**FIGURE 7** Percent of Phase 2 and 3 disease-modifying therapy trials requiring amyloid evidence (positron emission tomography, cerebrospinal fluid or either) at entry: 2016–2020 (ClinicalTrials.gov accessed February 27, 2020) (Figure by Mike de la Flor)

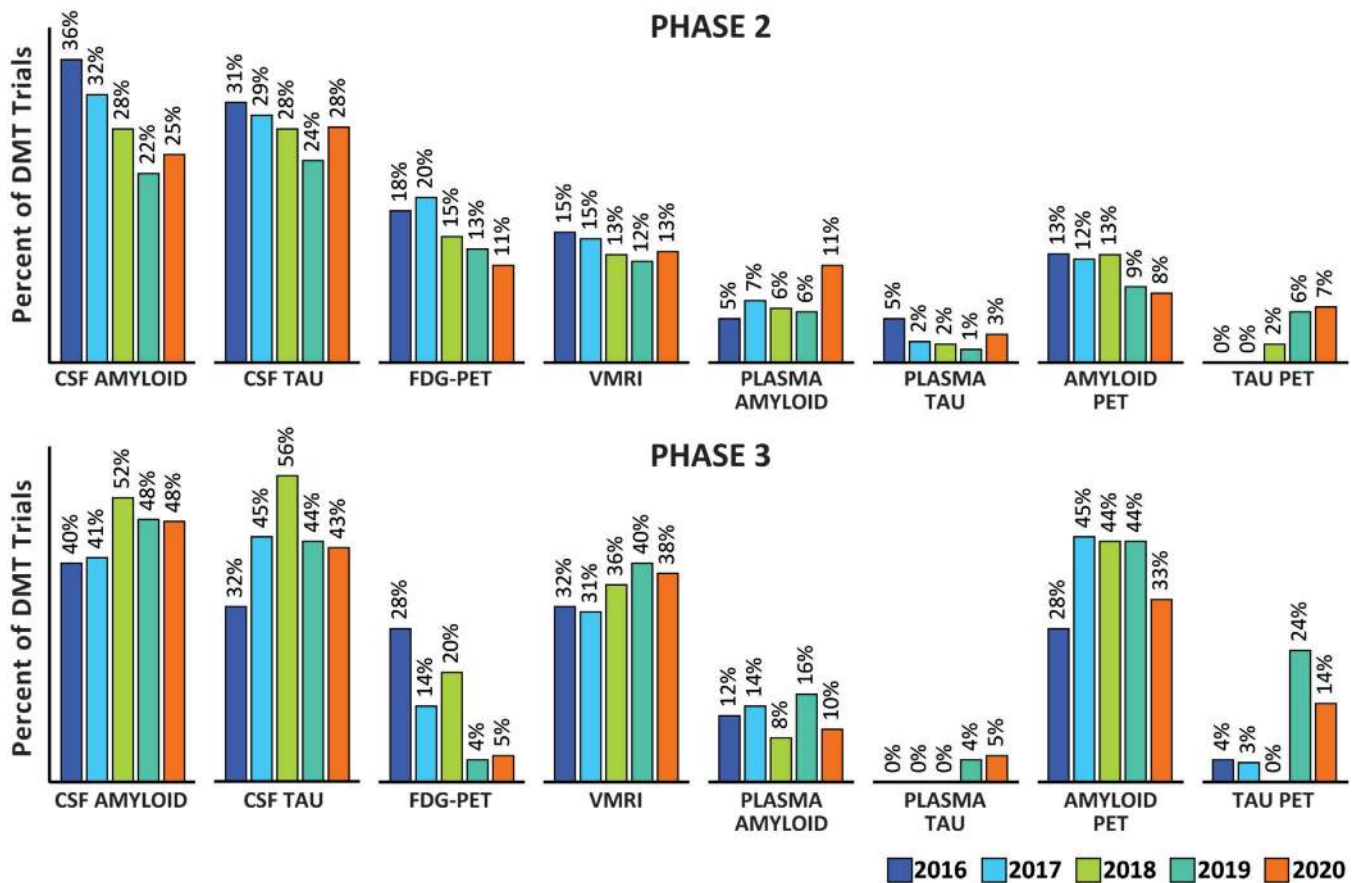
Similarly, substantiation of disease-modifying effects is expected to rely on a combination of clinical trial design, clinical outcome measures, and biomarkers of AD, especially markers of neurodegeneration.<sup>9</sup> Figure 8 shows the 5-year trend in use of biomarkers as outcomes in

trials of disease modifying agents. The number of trials of DMTs not using biomarkers for diagnostic confirmation, demonstration of target engagement, and support of disease modification is surprisingly high.

Basket trials can improve efficiency by including more than one disorder that has a characteristic biomarker or endophenotype.<sup>53</sup> TPI-287 was assessed in a basket trial comprised of patients with tau pathology including AD, PSP, and corticobasal degeneration.<sup>54</sup> The trial of pimavanserin used a basket trial strategy with five types of dementia. Basket trials can facilitate recruitment by having less narrow inclusion criteria, provide insight into the responsiveness of different conditions to the intervention, and facilitate understanding of the biology of the diseases involved in the studies.<sup>53</sup>

The World Health Organization registry indicates that there are 170 drugs in development for AD worldwide, contrasting with 6833 for malignant neoplasms and 433 for diabetes. These disparities reflect the less well defined target biology, limited availability of biomarkers, longer trial durations, greater expense, and higher risk of failure of AD drug development programs.

In summary, there are fewer agents in the AD pipeline in 2020 than in 2019 (121 vs 134). There are 29 agents in Phase 3 (compared to 29 in 2019), 65 agents in Phase 2 (compared to 75 in 2019), and 27 in Phase 1 (compared to 30 in 2019). All BACE inhibitors—prominent in the 2019 pipeline—have been discontinued for futility or toxicity.



**FIGURE 8** Phase 2 and Phase 3 disease-modifying therapy trials using Alzheimer's disease biomarkers as outcome measures: 2016–2020 (ClinicalTrials.gov accessed February 27, 2020) (Figure by Mike de la Flor)

Several agents have shown robust reductions of amyloid using amyloid PET and new trials will provide insight into the relationship of anti-amyloid and clinical effects. Biomarkers provide increasing data linking the MOA of the candidate agent to the biology of AD and promise to inform drug development decisions. The 5-year perspective captured in this pipeline review shows that over this period there have been trends for increased pipeline target diversity, greater reliance on repurposed agents, engagement of participants in more mild stages of the continuum of AD with a corresponding change of trial entry criteria and outcome measures, and increasing use of biomarkers to define trial populations.

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## CONFLICTS OF INTEREST

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