Preclinical Alzheimer Disease Drug Development: Early Considerations Based on Phase 3 Clinical Trials

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SUMMARY

The number of people in the United States living with Alzheimer disease (AD) is growing, resulting in significant clinical and economic impact. Substantial research investment has led to drug development in stages of AD before symptomatic dementia, such as preclinical AD. Although there are no treatments approved for preclinical AD, there are currently 6 phase 3 clinical trials for preclinical AD treatments. In this article, we review these clinical trials and highlight considerations for future coverage decisions.

In line with the definition of preclinical AD, enrollment in these trials focuses on cognitively unimpaired patients that are at high risk of AD because of family history and then genetic testing or brain imaging. Enrollment in most of these trials also allows for younger patients, including those aged under 65 years. Primary clinical trial endpoints focus on cognition often 4 or more years after treatment. Secondary endpoints include other measures of cognition and function, as well as biomarkers.

Review of these trials brings to light a few potential considerations when covering these new medications in the future. First, novel and potentially costly approaches involving genetic testing and/or positron emission tomography imaging may be needed to identify appropriate patients and should be developed efficiently. Second, the long duration of these clinical trials suggest that there may be a need for alternative payment approaches in the United States that encourage early payers to pay for a medication for which the long-term benefits may not be realized until after the beneficiary is no longer with the health plan. Third, the value of AD treatments may differ across populations, creating a potential role for indication-based or population-based contracting. Finally, considering the potentially high budgetary impact and little real-world evidence for a new drug class, payers and manufacturers may want to consider outcomes-based payment approaches and coverage with evidence development to mitigate uncertainty about the value of the treatment demonstrated in well-defined populations in clinical trials versus more heterogeneous real-world settings.

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Alzheimer disease (AD) is the most common form of dementia, with an estimated prevalence between 10% and 30% in the population aged 65 years and above.^{1,2} The cost of health care and long-term care for individuals with AD or other dementias is high, estimated between \$159 billion to \$215 billion in 2010.² These costs are projected to more than double because of the aging of the population by 2040.²

There are currently 5 drug products approved by the U.S. Food and Drug Administration (FDA) that are available for the treatment of symptomatic dementia: donepezil, rivastigmine, galantamine, memantine, and a combination drug product

with donepezil and memantine. Donepezil and rivastigmine are approved by the FDA for mild, moderate, and severe dementia due to AD; galantamine is approved for mild to moderate dementia due to AD; and memantine is approved for moderate to severe dementia.³⁻⁶ None of these drugs slow the progression of the disease; instead, they relieve symptoms by increasing the amount of neurotransmitters in the brain. However, in most cases, their efficacy at relieving symptoms is moderate at best and limited in duration, and efficacy varies across patient groups, leaving AD patients and their families with few options for treatment.⁷⁻⁹

Reflecting this need and insights into potential new treatment mechanisms, there has been a 5-fold increase in investment to develop drugs that modify disease progression since 2011.¹⁰ In 2020 alone, the National Institutes of Health are expected to spend \$2.8 billion on AD research.⁹ Some researchers believe that to slow disease progression and preserve brain function, treatments may be more effective if given earlier in the disease process.¹¹ Some of these drugs are currently being developed to target stages of AD before symptomatic dementia.

According to the National Institute on Aging (NIA) and Alzheimer's Association (AA) framework, there are 2 stages before mild, moderate, and severe dementia due to AD: (1) preclinical, when symptoms are not yet present but brain changes have begun, and (2) mild cognitive impairment (MCI) due to AD (also called prodromal AD), which is characterized by brain changes and mild cognitive symptoms that do not significantly affect everyday living.¹²⁻¹⁴ It should be noted that the 2018 update to the NIA-AA framework was intended for research and not routine care, but MCI is diagnosed in routine care based on criteria that were developed in 2011.^{13,15}

If successful and approved for an earlier stage of AD, the drugs that are in development could have a major impact on the care of AD. These medicines could also have substantial effects on the timing and nature of AD-related costs, with significant implications for federal and state programs and commercial insurance. In this article, we review the phase 3 clinical trials for preclinical AD and highlight potential implications for future payer coverage decisions.

Phase 3 Clinical Trials for Preclinical Alzheimer Disease

As of 2019, there were 6 phase 3 clinical trials targeting the preclinical stage of AD, with estimated study end dates that

TABLE 1 Summary of Phase 3 Preclinical Alzheimer Disease Clinical Trials

Clinical Trial (estimated enrollment) [Sponsor]	Drugs [Drug Class/Type (Mechanism of Action)]	Inclusion	Exclusion	Primary Endpoint [Measurement Time Frame]	Secondary Endpoints [Measurement Time Frame]	Start and (estimated) End Date
Targeting Preclinical Stage Only						
NCT02008357 (n = 1,150) [Eli Lilly and Company] ¹⁷	Solanezumab [Monoclonal antibody (anti-amyloid)]	Age 65-85 years Has a Mini-Mental State Examination (MMSE) score at screening of 25 to 30. Has a global Clinical Dementia Rating (CDR) scale score at screening of 0. Has a Logical Memory II score at screening of 6 to 18. Has a florbetapir PET scan that shows evidence of brain amyloid pathology at screening. Has a study partner that is willing to participate as a source of information and has at least weekly con- tact with the participant (contact can be in-person, via telephone or electronic communication).	Is receiving a prescription acetylcholinesterase inhibitor (AChEI) and/or memantine at screening or baseline. Lacks good venous access, such that intravenous drug delivery or multiple blood draws would be precluded. Has current serious or unstable illness including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic, psychiatric, immunologic, or hematologic disease or other conditions that, in the investi- gator's opinion, could interfere with the analyses of safety and efficacy in this study. Has had a history within the last 5 years of a serious infec- tious disease affecting the brain (including neurosyphilis, men- ingitis, or encephalitis) or head trauma resulting in protracted loss of consciousness. Has had a history within the last 5 years of a primary or recurrent malignant disease with the exception of any in situ cancer that was appro- priately treated and is being appropriately monitored, such as resected cutaneous squa- mous cell carcinoma in situ or in situ prostate cancer with normal prostate-specific anti- gen post-treatment. Has a known history of human immunodeficiency virus, clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis). Is clinically judged by the investigator to be at serious risk for suicide. Has a history within the past 2 years of major depression or bipolar disorder as defined by the most current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Has a history within the past 5 years of chronic alcohol or drug abuse/dependence as defined by the most current version of the DSM.	Change from Baseline of the Preclinical Alzheimer Cognitive Composite (PACC) [Time Frame: Baseline, Week 240; Baseline, Week 336]	1. Change from Baseline in Cognitive Function Index (CFI) [Time Frame: Baseline, Week 240; Baseline, Week 336] 2. Change from Baseline in Alzheimer's Disease Cooperative Study— Activities Daily Living—Prevention Questionnaire (ADCS-ADL- Prevention Questionnaire) Score [Time Frame: Baseline, Week 240; Baseline, Week 336] 3. Change from Baseline in Mean Composite Standardized Uptake Value Ratio (SUVR) [Time Frame: Baseline, Week 240] 4. Change from Baseline in Cerebrospinal Fluid (CSF) Tau Biomarkers [Time Frame: Baseline, Week 240] 5. Change from Baseline of CSF Concentrations of Amyloid Beta (Abeta) [Time Frame: Baseline, Week 240] 6. Change from Baseline of Volumetric Magnetic Resonance Imaging (vMRI) [Time Frame: Baseline, Week 240] 7. Change from Baseline on the Clinical Dementia Rating—Sum of Boxes score (CDR-SB) [Time Frame: Baseline, Week 336] 8. Change from Baseline on the Computerized Cognitive Composite (C3) [Time Frame: Baseline, Week 336]	February 2014 & July 2022

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TABLE 1 Summary of Phase 3 Preclinical Alzheimer Disease Clinical Trials (continued)

Clinical Trial (estimated enrollment) [Sponsor]	Drugs [Drug Class/Type (Mechanism of Action)]	Inclusion	Exclusion	Primary Endpoint [Measurement Time Frame]	Secondary Endpoints [Measurement Time Frame]	Start and (estimated) End Date
NCT02565511 ^a (n = 481) [Novartis] ¹⁸	CAD106, CNP520 [Amyloid vaccine and BACE inhibitor (anti-amyloid)]	<p>Consent to receive disclosure of their risk estimates to develop clinical symptoms of AD based on their APOE genotype.</p> <p>Male or female, age 60 to 75 years inclusive. Females must be considered post-menopausal and not of child bearing potential.</p> <p>Mini-Mental State Examination (MMSE) total score ≥ 24 (at screening or in previous 3 months) and cognitively unimpaired as evaluated by memory tests performed at screening.</p> <p>Homozygous APOE4 genotype.</p> <p>Participant's willingness to have a study partner.</p>	<p>Any disability that may prevent the participants from completing all study requirements.</p> <p>Current medical or neurological condition that might impact cognition or performance on cognitive assessments.</p> <p>Advanced, severe progressive or unstable disease that may interfere with the safety, tolerability and study assessments, or put the participant at special risk.</p> <p>History of malignancy of any organ system, treated or untreated, within the past 60 months.</p> <p>History of hypersensitivity to any of the investigational drugs or their excipients/adjuvant or to drugs of similar chemical classes.</p> <p>Indication for, or current treatment with ChEIs and/or another AD treatment (e.g., memantine).</p> <p>Contraindication or intolerance to MRI or PET investigations (with fluorinated radio ligands).</p> <p>Brain MRI results showing findings unrelated to AD that, in the opinion of the Investigator might be a leading cause to future cognitive decline, might pose a risk to the participant, or might prevent a satisfactory MRI assessment for safety monitoring.</p> <p>Suicidal Ideation in the past 6 months, or Suicidal Behavior in the past 2 years.</p> <p>A positive drug screen at Screening, if, in the investigator's opinion, this is due to drug abuse.</p> <p>Significantly abnormal laboratory results at Screening, or infection not as a result of a temporary condition.</p> <p>Current clinically significant ECG findings.</p> <p>For Cohort - I only: Participants with previous organ transplantation or stem cell transplantation, or indication for treatment with anti-coagulants.</p> <p>For Cohort - II only: Participants with depigmenting or hypopigmenting conditions (e.g., albinism vitiligo) or active/history of chronic urticarial in the past year.</p>	<p>Time to diagnosis of MCI due to AD or dementia due to AD [Time Frame: Through study completion, an average of 5 years]</p> <p>Change in the Alzheimer's Prevention Initiative Composite Cognitive (APCC) Test Score [Time Frame: Baseline to Month 60]</p>	<ol style="list-style-type: none"> 1. Change in Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score [Time Frame: Baseline to Month 60] 2. Number of participants with Adverse Events as a measure of Safety and Tolerability [Time Frame: Through study completion, an average of 5 years] 3. Change on the Total Scale score and individual neurocognitive domain index scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [Time Frame: Baseline to Month 60] 4. Change in the Everyday Cognition scale (ECog) total scores [Time Frame: Baseline to Month 60] 5. Change in AD-related biomarkers [Time Frame: Baseline to Months 24 and 60] 6. Change in APCC Test Score [Time Frame: Month 6 to Month 60] 7. Change in CDR-SOB [Time Frame: Month 6 to Month 60] 8. A beta-specific immune response [Time Frame: Through study completion, an average of 5 years] 	November 2015 & March 2025

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TABLE 1 Summary of Phase 3 Preclinical Alzheimer Disease Clinical Trials (continued)

Clinical Trial (estimated enrollment) [Sponsor]	Drugs [Drug Class/Type (Mechanism of Action)]	Inclusion	Exclusion	Primary Endpoint [Measurement Time Frame]	Secondary Endpoints [Measurement Time Frame]	Start and (estimated) End Date
NCT03131453 ^a (n = 1,145) [Novartis] ¹⁹	CNP520 [BACE inhibitor (anti-amyloid)]	Consent to receive disclosure of their risk estimates to develop clinical symptoms of AD based on their APOE genotype and, if Heterozygotes, evidence of elevated brain amyloid. Male or female, age 60 to 75 years inclusive. Females must be considered postmenopausal and not of child bearing potential. Cognitively unimpaired as evaluated by memory tests performed at screening. Participant's willingness to have a study partner. Carrier of at least one APOE4 gene if Heterozygotes, elevated brain amyloid (as measured by CSF Abeta or amyloid PET imaging).	Any disability that may prevent the participants from completing all study requirements. Current medical or neurological condition that might impact cognition or performance on cognitive assessments. Advanced, severe progressive or unstable disease that may interfere with the safety, tolerability and study assessments, or put the participant at special risk. History of malignancy of any organ system, treated or untreated, within the past 60 months. Indication for, or current treatment with, ChEIs and/or another AD treatment (e.g., memantine). Contraindication or intolerance to MRI. Brain MRI results showing findings unrelated to AD that, in the opinion of the Investigator might be a leading cause to future cognitive decline, might pose a risk to the participant, or might prevent a satisfactory MRI assessment for safety monitoring. Suicidal Ideation in the past 6 months, or Suicidal Behavior in the past 2 years. A positive drug screen at Screening, if, in the Investigator's opinion, this is due to drug abuse. Significantly abnormal laboratory results at Screening, not as a result of a temporary condition. Current clinically significant ECG findings. Clinically relevant depigmenting or hypopigmenting conditions (e.g., albinism, vitiligo) or active/history of chronic urticaria in the past year.	1. Time to event [Time Frame: Through study completion, at least 5 years], where event is defined as diagnosis of MCI due to AD or dementia due to AD, whichever occurs first during the course of the study, after confirmation by the adjudication committee 2. Change in the Alzheimer's Prevention Initiative Composite Cognitive (APCC) Test Score [Time Frame: Baseline to Month 60]	1. Change in Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score [Time Frame: Baseline to Month 60] 2. Change on the Total Scale score and individual neurocognitive domain index scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [Time Frame: Baseline to Month 60] 3. Change in the Everyday Cognition scale (ECog) total scores [Time Frame: Baseline to Month 60] 4. Change in cerebral amyloid angiopathy (CAA) [Time Frame: Through study completion, at least 5 years] 5. Change on volume of brain regions [Time Frame: Baseline to Month 60] 6. Change in amyloid deposition as measured by standardized uptake ratio (SUVR) of PET scan with amyloid radiotracer [Time Frame: Baseline to Months 24 and 60] 7. Change in CSF levels of Aβ ₄₀ , Aβ ₄₂ [Time Frame: Baseline to Months 24 and 60] 8. Change in CSF levels of total tau and phosphorylated tau [Time Frame: Baseline to Months 24 and 60] 9. Number of participants with adverse events as a measure of safety [Time Frame: Through study completion, at least 5 years]	August 2017 & March 2025 ^b

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TABLE 1 Summary of Phase 3 Preclinical Alzheimer Disease Clinical Trials (continued)

Clinical Trial (estimated enrollment) [Sponsor]	Drugs [Drug Class/Type (Mechanism of Action)]	Inclusion	Exclusion	Primary Endpoint [Measurement Time Frame]	Secondary Endpoints [Measurement Time Frame]	Start and (estimated) End Date
NCT02719327 ^a (n = 150) [VA Office of Research and Development] ²⁰	Icosapent ethyl [Purified form of omega-3 fatty acid EPA (neuro- protection)]	U.S Veteran eligible for VA care. Age 50-75 years, inclusive. Cognitively healthy. With increased risk for developing AD due to parental history of the dis- ease and increased preva- lence of APOE4 allele.^c	Dementia or mild cognitive impairment on screening evaluation. Current use of fish oil supple- ments (requires 3 month wash-out period). Active liver disease with AST or ALT greater than twice the upper limit of normal. Elevated creatine kinase greater than twice the upper limit of normal. Prior adverse reaction to statins or fish oil. Pregnant, nursing, or preg- nancy planned. Use of medications that inter- act with icosapent ethyl. Current use of anticoagulants. Known hypersensitivity to fish and/or shellfish. Current use of other investiga- tional drug. History of significant athero- sclerotic cardiovascular disease or diabetes mellitus. Low-density lipoprotein cholesterol ≥ 190 mg/dL or <80 mg/dL. Triglycerides ≥ 500 mg/dL. Creatinine >1.8 mg/dL. Previous lumbar surgery with contraindication to lumbar puncture. Claustrophobia requiring seda- tion for MRI. Pacemaker or other contraindi- cation for MRI. Consumption of >200 mg per day omega-3 fatty acids in diet.	Regional cerebral blood flow using arterial spin- labeling MRI [Time Frame: 18 month]	10. Change in neuro- fibrillary tangle bur- den as measured by standardized uptake ratio (SUVR) of PET scans with tau radio- tracer (where avail- able) [Time Frame: Baseline to Months 24 and 60] Cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease [Time Frame: 18 months], including CSF beta-amyloid, total tau, and phos- phorylated tau Cognitive perfor- mance [Time Frame: 18 months], mea- sured by Preclinical Alzheimer's Cognitive Composite (PACC)	June 2017 & November 2021
NCT02913664 ^a (n = 640) [University of Texas Southwestern Medical Center] ²¹	Losartan, amlodipine, atorvastatin [Angiotensin II receptor blocker, calcium chan- nel blocker, cholesterol agent (neuroprotec- tion through improvement in cardiovascular health)]	1. Age 60-85, all races/eth- nicities, and both sexes are eligible. 2. a) A positive family his- tory of dementia defined as having at least one first- degree relative with a his- tory of AD or other type of dementia, or b) having sub- jective cognitive decline.	1. Clinically documented history of stroke, focal neu- rological signs or other major cerebrovascular diseases based on clinical judgment or MRI/ CT scans such as evidence of infection, infarction or other brain lesions.	Change in global neurocognitive function	1. Domain-specific neurocognitive function assessed by using the tests included in the ADCS-PACC and NIH-TB Cognition. [Time Frame: 2 Years]	September 2016 & September 2022

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TABLE 1 Summary of Phase 3 Preclinical Alzheimer Disease Clinical Trials (continued)

Clinical Trial (estimated enrollment) [Sponsor]	Drugs [Drug Class/Type (Mechanism of Action)]	Inclusion	Exclusion	Primary Endpoint [Measurement Time Frame]	Secondary Endpoints [Measurement Time Frame]	Start and (estimated) End Date
		<p>3. Mini-Mental State Exam (MMSE) ≥ 26 to exclude gross dementia.</p> <p>4. Must lead a sedentary lifestyle defined by not having an "active" rating on Rapid Assessment of Physical Activity (RAPA), i.e., score below 6 on RAPA.</p> <p>5. a) Individuals treated for HTN with $110 \leq \text{SBP} \leq 130$ mmHg; or b) Individuals with $\text{SBP} > 130$ and $\text{SBP} < 180$ (If an individual, not treated for HTN, has a $\text{SBP} \geq 125$ mmHg, consider rescreening after 24 hours).</p> <p>6. Willingness to be randomized into the treatment groups and ability to return to clinic for follow-up visits over 24 months.</p> <p>7. Fluency in English, adequate visual and auditory acuity to allow neuropsychological testing.</p> <p>8. Participants must have a regular health care provider.</p> <p>9. Physical ability to undergo exercise training; able to walk 10 minutes without pain.</p>	<p>2. Diagnosis of AD or other type of dementia, or significant neurologic diseases such as Parkinson disease, seizure disorder, multiple sclerosis, history of severe head trauma or normal pressure hydrocephalus.</p> <p>3. Evidence of severe major depression ($\text{GDS} > 12$, may be rescreened after 12 weeks or longer if evidence of reactive depression or temporary mood disturbances) or clinically significant psychopathology (e.g., psychosis and schizophrenia); if hospitalized in past year, can be rescreened in 6 months; or presence of a major psychiatric disorder that in the investigator's opinion, could interfere with adherence to research assessments or procedures.</p> <p>4. Unstable heart disease based on clinical judgment (e.g., heart attack/cardiac arrest, cardiac bypass procedures within previous 6 months and congestive heart failure) or other severe medical conditions.</p> <p>5. History of atrial fibrillation and evidence on ECG with any of the following: active symptoms of persistent palpitation, dizziness, history of syncope, chest pain, dyspnea, orthopnea, shortness of breath at rest, or paroxysmal nocturnal dyspnea within the past 6 months; resting heart rate of < 30 or > 110 bpm; taking class I or III anti-arrhythmic drugs including flecainide, propafenone, dronedarone, sotalol, dofetilide, and amiodarone; or clinical concerns for safely participating in exercise and lowering blood pressure.</p> <p>6. Systolic BP equal or greater than 180 mmHg and/or diastolic BP equal or greater than 110 mmHg, may be rescreened in 1 week.</p> <p>7. Orthostatic hypotension, defined as the third standing $\text{SBP} < 100$ mmHg, may be rescreened after 2 weeks.</p> <p>8. History of significant autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, or polymyalgia rheumatic.</p> <p>9. Significant history of alcoholism or drug abuse within the last 5 years.</p>	<p>[Time Frame: 2 Years], as measured by Alzheimer's Disease Cooperative Study-Preclinical Alzheimer Cognitive Composite (ADCS-PACC) and NIH Toolbox (NIH-TB) Cognition Battery</p>	<p>2. Whole brain and hippocampal volume assessed via Magnetic Resonance Imaging (MRI). [Time Frame: 2 years]</p> <p>3. Global and regional brain perfusion assessed via MRI. [Time Frame: 2 years]</p> <p>4. Brain white matter hyperintensity (WMH) assessed via MRI. [Time Frame: 2 years]</p> <p>5. Brain white matter microstructural integrity assessed via MRI. [Time Frame: 2 years]</p> <p>6. Brain neural network functional connectivity assessed via functional MRI. [Time Frame: 2 years]</p> <p>7. Patient-reported outcomes (PRO) of mental and physical health and health-related quality of life assessed by using NIH PROMIS. [Time Frame: 2 years]</p> <p>8. Physical function assessed via the Short Physical Performance Battery (SPPB). [Time Frame: 2 years]</p> <p>9. Dual task performance assessed via distracted and non-distracted 10-meter walk. [Time Frame: 2 years]</p>	

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TABLE 1 Summary of Phase 3 Preclinical Alzheimer Disease Clinical Trials (continued)

Clinical Trial (estimated enrollment) [Sponsor]	Drugs [Drug Class/Type (Mechanism of Action)]	Inclusion	Exclusion	Primary Endpoint [Measurement Time Frame]	Secondary Endpoints [Measurement Time Frame]	Start and (estimated) End Date
			<p>10. Uncontrolled diabetes mellitus, defined as hemoglobin A1c > 7.5%, or requiring insulin treatment.</p> <p>11. Regularly smoking cigarette within the past year.</p> <p>12. Women with a potential for pregnancy, lactation/child bearing (2-year post-menopausal or surgically sterile to be considered not child bearing potential).</p> <p>13. Participant enrolled in another investigational drug or device study, either currently or within the past 2 months.</p> <p>14. Severe obesity with BMI ≥ 45; clinical judgment should be applied in all cases to assess patient safety and anticipated compliance.</p> <p>15. Allergy to angiotensin receptor blockers (ARBs), i.e., drugs that have a suffix “-sartan.”</p> <p>16. Allergy to other study drugs or their ingredients; for example, clinical history or self-reported allergy or intolerance to atorvastatin.</p> <p>17. Abnormal screening laboratory tests (e.g., liver ALT and AST > 3 $\times$ ULN, CK > 3 $\times$ ULN, GFR < 30 or Hct < 28%); may be rescreened after 2 weeks or longer.</p> <p>18. A medical condition likely to limit survival to less than 3 years.</p> <p>19. Participant has any conditions judged by the study investigator to be medically inappropriate, risky or likely to cause poor study compliance. For example:</p> <ul style="list-style-type: none"> a. Plans to move outside the clinic catchment area in the next 2 years. b. Significant concerns about participation in the study from spouse, significant other, or family members. c. Lack of support from primary health care provider. d. Residence too far from the study clinic site such that transportation is a barrier including persons who require transportation assistance provided by the study clinic funds for screening or randomization visits. e. Residence in a nursing home; persons residing in an assisted living or retirement community are eligible if they meet the other criteria. 			

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TABLE 1 Summary of Phase 3 Preclinical Alzheimer Disease Clinical Trials (continued)

Clinical Trial (estimated enrollment) [Sponsor]	Drugs [Drug Class/Type (Mechanism of Action)]	Inclusion	Exclusion	Primary Endpoint [Measurement Time Frame]	Secondary Endpoints [Measurement Time Frame]	Start and (estimated) End Date
			f. Other medical, psychiatric, or behavioral factors that, in the judgment of the site PI or clinician, may interfere with study participation or the ability to follow the study protocol. g. Couples or significant partners who live together cannot be enrolled or participate simultaneously in the study. 20. Lack of approval from participant's regular health care providers, i.e., a signed letter of agreement for the participants to be enrolled in rAD.			
Targeting Preclinical, Prodromal, or Mild Stages of AD						
NCT01760005 ^a (n = 490) [Washington University School of Medicine] ²²	Gantenerumab, solanezumab [Monoclonal antibody (anti-amyloid)]	Between 18-80 years of age Individuals who know they have an AD-causing mutation or are unaware of their genetic status and have an autosomal dominant Alzheimer disease mutation in their family. Are within -15 to +10 years of the predicted or actual age of cognitive symptom onset for treatment arms. For Cognitive Run-In: includes participants who are younger than 15 years prior to the expected age of cognitive symptom onset, in addition to those 15 years younger and no more than 10 years older than expected or actual age of cognitive symptom onset. Cognitively normal or with mild cognitive impairment or mild dementia, Clinical Dementia Rating (CDR) of 0-1 (inclusive). Fluency in DIAN-TU trial approved language and evidence of adequate premorbid intellectual functioning. Able to undergo MRI, Lumbar Puncture (LP), PET, and complete all study related testing and evaluations. For women of childbearing potential, if partner is not sterilized, subject must agree to use effective contraceptive measures (hormonal contraception, intra-uterine device, sexual abstinence, barrier method with spermicide).	History or presence of brain MRI scans indicative of any other significant abnormality. Alcohol or drug dependence currently or within the past 1 year. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin or body which would preclude MRI scan. History or presence of clinically significant cardiovascular disease, hepatic/renal disorders, infectious disease or immune disorder, or metabolic/endocrine disorders Anticoagulants except low dose (≤ 325 mg) aspirin. Have been exposed to a monoclonal antibody targeting beta amyloid peptide within the past 6 months. History of cancer within the last 5 years, except basal cell carcinoma, non-squamous skin carcinoma, prostate cancer or carcinoma in situ with no significant progression over the past 2 years. Positive urine or serum pregnancy test or plans or desires to become pregnant during the course of the trial. Subjects unable to complete all study related testing, including implanted metal that cannot be removed for MRI scanning, required anticoagulation and pregnancy.	Assess cognitive efficacy in individuals with mutations causing dominantly inherited AD as measured by change in the DIAN-TU cognitive composite score. [Time Frame: Baseline and Weeks 52, 104, 156, and 208]	1. Gantenerumab: Cerebral amyloid imaging using [11C] PiB-PET. [Time Frame: Baseline and Weeks 52, 104, and 208] 2. Solanezumab: Total Abeta 1-42 (A β 42) in CSF. [Time Frame: Baseline, Week 104 and Week 208] 3. Change from Baseline in Clinical Measures [Time Frame: Baseline, week 208]: Clinical Dementia Rating (CDR), including CDR sum of boxes (CDR-SB) and clinician's diagnostic assessment Geriatric Depression Scale (GDS) Neuropsychiatric Inventory Questionnaire (NPI-Q) Functional Assessment Scale (FAS) Mini Mental Status Exam (MMSE) 4. Change from Baseline in Cognitive Measures [Time Frame: Baseline, week 208]: International Shopping List Test (12-Item Word List Learning): 3 learning trials, Immediate Recall, 30-min Delayed Recall (CogState)	December 2012 & March 2021

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TABLE 1 Summary of Phase 3 Preclinical Alzheimer Disease Clinical Trials (continued)

Clinical Trial (estimated enrollment) [Sponsor]	Drugs [Drug Class/Type (Mechanism of Action)]	Inclusion	Exclusion	Primary Endpoint [Measurement Time Frame]	Secondary Endpoints [Measurement Time Frame]	Start and (estimated) End Date
		Adequate visual and auditory abilities to perform all aspects of the cognitive and functional assessments. Has a Study Partner who in the investigator's judgment is able to provide accurate information as to the subject's cognitive and functional abilities, who agrees to provide information at the study visits which require informant input for scale completion.			Groton Maze Learning Test: Timed Chase Task, 5 learning Trials, Immediate Recall, 30-min Delayed Recall (CogState) Cogstate Detection Task Cogstate Identification Test Cogstate One Card Learning Test Cogstate One-Back (OBK) Task Behavioral Pattern Separation Object Task Memory Complaint Questionnaire (MAC-Q) Trails A & B Wechsler Memory Scale - Revised (WMS-R) Digit Span Wechsler Adult Intelligence Scale - Revised (WAIS-R) Digit-Symbol Substitution Test Raven's Progressive Matrices (Set A) Category Fluency (Animals & Vegetables) Wechsler Memory Scale Logical Memory I Paragraph Memory (Immediate & Delayed Recall)	

^aPhase 2/3.

^bCurrently, Clinicaltrials.gov reports the recruitment status for this trial as "Active, not recruiting"; however, there has been notice that the sponsor will be terminating the study (<https://www.fiercebitech.com/biotech/weak-data-spur-amgen-novartis-to-can-pivotal-alzheimer-s-test>).

^cPer study description.

AD=Alzheimer disease; A1c=hemoglobin A1c; APOE4=apolipoprotein E4; BMI=body mass index; HTN=hypertention; MCI=mild cognitive impairment; MRI=magnetic resonance imaging; PET=positron emission tomography; rrAD=risk reduction for Alzheimer disease; VA=Department of Veterans Affairs.

range from 2021 to 2025 (Table 1).¹⁶⁻²² Four of these 6 trials involve drugs that target amyloid (e.g., remove amyloid and/or prevent aggregation or production). The other 2 drugs aim for neuroprotection either directly or through improving cardiovascular health.¹⁶ One of the clinical trials is enrolling patients not only in the preclinical stage, but also in the MCI and mild dementia stages of AD.²¹

Clinical Trial Populations

The 6 clinical trials are enrolling patients at high risk for AD based on family history, presence of apolipoprotein E4 (apoE4) gene, or elevated brain amyloid through positron emission tomography (PET) scan or cerebrospinal fluid (CSF; Table 1).

All 6 clinical trials require that enrolled patients are cognitively unimpaired, with normal scores on tests such as the Mini-Mental State Examination. The 1 exception is a trial targeting not only preclinical AD, but also MCI and mild dementia.

Enrollment in most of these trials is restricted to relatively healthy patients, such as those without serious or unstable illness. Patients also cannot have a recent history (within the last few years) of cancer, serious brain infection, or head trauma and must not already be on an AD treatment. Enrollment generally excludes individuals with a recent history of mental health issues (e.g., suicide, depression, and bipolar disorder) or substance abuse problems. Because of the nature of certain endpoints, patients must be able to undergo

magnetic resonance imaging (MRI) and, therefore, not have pacemakers or artificial heart valves, as well as be willing to undergo lumbar punctures (for collection of CSF). Patients must also be fluent in English and have adequate visual and auditory function to allow neuropsychological testing.

Five of the 6 clinical trials include patients aged under 65 years (Table 1), while 1 trial expands beyond the preclinical stage of AD and includes patients aged as young as 18 years. The most common age ranges are 50 or 60 years to 75 or 85 years.

Clinical Trial Endpoints

All but 1 trial has a primary endpoint related to cognitive function (Table 1). However, across the trials, cognitive function is measured through different tests, such as the Preclinical Alzheimer Cognitive Composite (PACC), Alzheimer's Prevention Initiative Composite Cognitive (APCC) Test, Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) Cognitive Composite, and NIH Toolbox (NIH-TB) Cognition Battery. The majority of these endpoints (4 of 6 trials) were measured at baseline and again 4 or more years after start of treatment. However, some trials involved repeated measurements throughout the study period, and other primary endpoints were measured as time-to-event outcomes (Table 1). Additional primary endpoints include time to diagnosis of MCI or dementia because of AD. The 1 trial with a primary endpoint related to cerebral blood flow has a secondary endpoint related to cognitive function.

Common secondary endpoints include additional measures of cognitive function as reported in Table 1; biomarkers such as amyloid and tau levels and deposition, as measured through PET scans and/or CSF; other pathophysiologic changes associated with AD, such as brain white matter and perfusion abnormalities as measured through MRIs; and functional measures such as from the Alzheimer's Disease Cooperative Study-Activities Daily Living-Prevention Questionnaire (Table 1).

The combination of cognition, function, and biomarker endpoints in the trials is aligned with the FDA's perspective on developing drugs to be used in the earlier stages of AD. According to draft guidance, the FDA would ideally like to see that a drug used in the earlier stages of AD has an effect on functional and cognitive deficits and suggests trials with sufficient duration to achieve this.²³ Within the context of preclinical AD, the FDA draft guidance mentions that effects on characteristic pathophysiologic changes of AD, or biomarkers, could serve as the basis for accelerated approval.²³ However, at this time, there is insufficient evidence that an effect on biomarkers in AD will be reasonably likely to predict clinical benefit, which is the standard for accelerated approval.²³

Looking Ahead: Potential Coverage Considerations

Although no drugs have been approved for the preclinical stage of AD, review of the 6 ongoing phase 3 clinical trials raises

potential issues of which payers should be aware. First, if a drug for the preclinical stage of AD is approved in high-risk patients, identifying such patients for treatment may require substantial cost and effort.²⁴⁻²⁶ Currently, preclinical AD trials are identifying patients at increased risk through family history and then genetic testing or PET imaging. Genetic testing and PET imaging can pose barriers to patient identification. Although some genetic testing prices are declining, the large number of patients who may be eligible to receive genetic testing could lead to a high budgetary impact for the payer. Additionally, genetic testing may require the involvement of genetic counselors, which would lead to additional costs and perhaps further barriers because genetic counselors are also limited in supply. Yet another barrier is patient rejection of genetic testing because of the fear of such possible negative consequences as higher premiums when purchasing long-term insurance if discovered to be at high risk of certain conditions.

Similarly, PET imaging can be expensive, and patients may not want to undergo such testing. As a result, identifying appropriate patients for treatment may require new initiatives around education, screening, and follow-up. Such initiatives may involve multiple stakeholders and be costly. For example, electronic medical record vendors could play a role in developing screening algorithms. Providers could then play a role in implementing the education, screening, and follow-up; however, they would need financial incentives to perform these services.

Other technologies on the horizon could also help with screening, such as blood tests and retina scans. However, these technologies are still being tested, and it remains unknown whether they will replace the use of PET imaging.^{27,28} If successful, a combination of these technologies alongside assessing family history, genetic testing, and PET testing could be used to develop an approach to screen patients at high risk for preclinical AD.

Second, the majority of clinical trials involve patients aged under 65 years and measure cognitive function 4 or more years later. If treatment is approved in a pre-Medicare population, but effects on cognition and function do not occur until many years later when patients have transitioned to another payer such as Medicare or Medicaid (for long-term care costs), some payers may be less willing to cover the medications. Therefore, there may be a need for alternative payment approaches or policy solutions to provide incentives for an earlier payer to cover medicines that may not increase health or delay costs until after the beneficiary has left the health plan. A similar problem occurred with hepatitis C virus treatments, and several payers reacted by implementing novel payment approaches.^{29,30}

Third, past literature has suggested heterogeneity in AD progression and etiology.^{31,32} Several of the preclinical AD trials discussed in this article focus on populations with specific genetic variants or mutations (e.g., homozygous apoE4

genotype, at least 1 apoE4 gene if heterozygote, and autosomal dominant AD mutation). This may result in drug treatments that are approved with narrow and differing indications. If there are major differences in the treatment effect for one indication versus another, payers may consider indication-based pricing contracts that vary payment based on the value associated with each indication,^{33,34} or other alternatives to volume-based contracts, such as a per-member per-month payment in a covered population.^{29,35}

Fourth, the clinical trials are excluding sicker populations with serious or unstable illness, recent history of mental health or substance abuse conditions, and inability or unwillingness to undergo CSF draws, MRI scanning, and/or genetic testing. Thus, the clinical trials do not reflect the mix of high-risk patients seen in the real-world setting, and the treatment effects seen in the clinical trial populations may not be the same as in sicker populations. Since the first of these medications would likely be a novel drug class that is administered long term, the budgetary impact could be very high. Payers would have added pressure to ensure that this medication was cost-effective. Therefore, payers and manufacturers may want to consider an outcomes-based payment arrangement that includes monitoring of cognition and function in patients receiving and adhering to the treatment to ensure that the drug brings value. They may also consider coverage accompanied by the conduct of additional “real world” clinical studies that develop better evidence on benefits in these populations, as well as additional evidence (e.g., on longer-term outcomes and functional outcomes) relevant to the value of these treatments.

In addition, depending on the efficacy and safety evidence of the treatments, individuals at elevated risk who do not meet the specific risk measures included in the trials, as well as individuals with lower risk, may want “off-label” coverage because they too expect some benefits from treatment. These benefits may not be as large as for the specific high-risk patients targeted in the trials, requiring larger and potentially more costly long-term studies to determine safety and effectiveness. Mechanisms for developing such evidence, and for coverage and payment policy while such evidence is being developed, may also require innovative approaches by payers and manufacturers, such as coverage with evidence development or “adaptive” payment approaches that adjust payments as evidence accumulates.³⁶

Conclusions

Disease-modifying drugs are being developed for use in the earlier stages of AD. The majority of ongoing, phase 3, preclinical AD trials include patients aged over a range of at least 60 to 75 years, with no cognitive impairment but at high risk of AD because of family history and specific genetic variations of AD or evidence of brain pathology through PET imaging. Most primary endpoints are related to cognition and are measured

through a variety of tests at 4 or more years. Secondary endpoints include biomarkers, other measures of cognition, and measures of function, which is aligned with FDA draft guidance recommendations.

Review of these trials brings to light a few potential considerations when covering new medications in the future: (a) new and potentially costly approaches involving blood-based biomarker testing, genetic testing and/or PET imaging may be needed to identify appropriate patients and should be developed efficiently; (b) there may be a need for alternative payment approaches that encourage payers to incur costs that may have no short-term financial benefits but may result in long-term benefit for patients; (c) the value of AD treatments may differ across populations, creating a potential role for population-based contracting; and (d) payers and manufacturers may want to consider outcomes-based payment approaches and coverage with evidence development to mitigate uncertainty about the value of the treatment demonstrated in well-defined populations in clinical trials versus more heterogeneous real-world settings.

Given the magnitude of the potential health and cost consequences associated with these new early interventions to address AD, further development of these approaches before the treatments come to market will enable payers, manufacturers, and policymakers to manage access and cost issues more effectively.

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