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Alzheimer's Disease: An Overview and Current Phase 3 Disease-Modifying Biologic Treatments

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Abstract: Alzheimer's Disease (AD) is a degenerative brain disease caused by cell damage leading to brain changes such as amyloid plaques and neurofibrillary tangles. Alois Alzheimer was a clinical psychiatrist and neuroanatomist in Germany who first discovered Alzheimer's Disease through microscopic viewing of Auguste D's brain. Through more research following Dr. Alzheimer's death, they began to stage AD. The six stages are: pre-clinical, mild, moderate, moderately severe, severe, and very severe. The current treatments approved by the FDA work to slow the progression of AD, rather than modify the disease. There are currently three Disease-Modifying Biologic clinical-trial drugs on the market for AD: Gantenerumab, Lecanemab, and Solanezumab, each with completed phase one and phase two trials and several phase three trials in progress.

One Sentence Summary: The research for a cure for Alzheimer's Disease is escalating, and disease-modifying biologic drugs are slowly making their way into clinical trials.

The purpose of this review paper is to give an overview, history, and the phase-three disease-modifying biologic treatments in clinical trials (gantenerumab, lecanemab, and solanezumab) for Alzheimer's Disease (AD). Globally, finding a cure for Alzheimer's Disease is continuously progressing. Although there are many medications on the market for Alzheimer's Disease, none have cured the disease, but rather, slowed down its progression. In the United States of America, Alzheimer's Disease is the fifth leading cause of death for those individuals over the age of 65 years old and the overall seventh leading cause of death in the United States behind heart disease, cancer, COVID-19, accidents, stroke, and chronic lower respiratory diseases (1, 2). AD currently affects more than six million citizens, and in 2050, it is estimated to affect approximately 13 million (1). Additionally, one in three seniors perishes from Alzheimer's Disease or other forms of dementia (1). These statistics bring to light the importance of finding a cure for AD.

According to the Alzheimer's Association, dementia is a "general term for loss of memory, language, problem-solving and other thinking abilities that are severe enough to interfere with daily life" (3). Diseases that fall under the term dementia include Alzheimer's Disease (60-80%), Lewy Body Dementia (5-10%), Vascular Dementia (5-10%), Frontotemporal Dementia (5-10%), Parkinson's Disease, Huntington's Disease, and Mixed Dementia (3).

Alzheimer's Disease

According to the Alzheimer's Association, AD is defined as a degenerative brain disease caused by cell damage leading to brain changes (4). Physiologically, the brain transforms by forming amyloid plaques, which are misfolded protein (amyloid-β) aggregates present in nerve junctions, preventing connections between nerve cells (5,6). Amyloid-β has several conformations in the brain when these plaques are overproduced, or clearance is inhibited (7). These may include soluble monomers, oligomers, protofibrils, insoluble fibrils, and plaque as seen in *Fig. 1* (8).

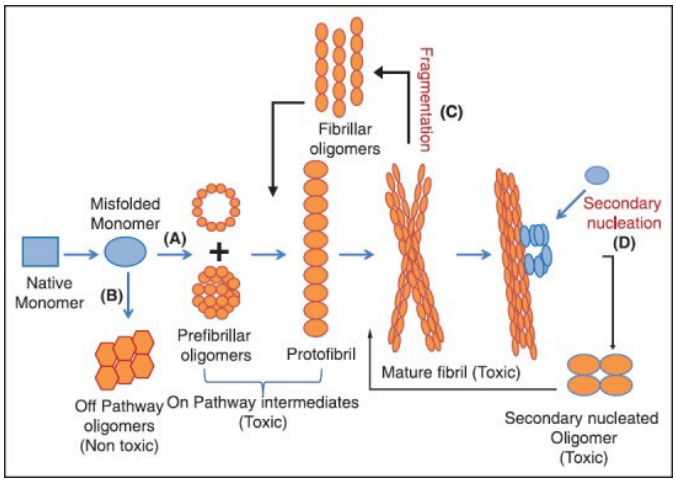

Fig. 1 *Conformations of Amyloid-β in Alzheimer's Disease (9)*

In addition to Amyloid-β plaques, fibrillary tangles are formed as seen in *Fig. 2* (6). Hyperphosphorylated tau, encoded by *MAPT* is the protein that functions to form the core of the Amyloid-β plaques and fibrillary tangles (6). *MAPT* is located on chromosome 17 and functions to assemble and stabilize microtubules in the cell (11). Microtubules work to maintain cell shape, assist in cell division, and transport materials within cells (11). In those individuals with AD, tau will detach from the microtubules and stick together, consequently forming threads and tangles of tau within neurons

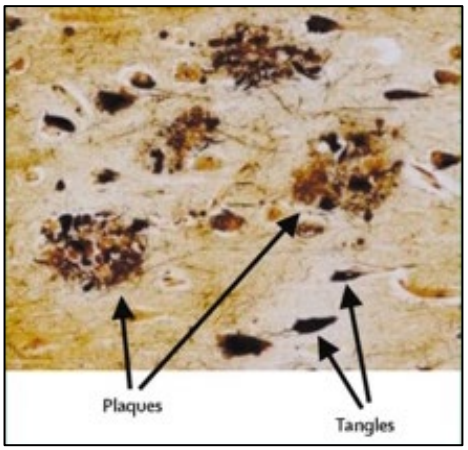

Fig. 2 *Amyloid-β plaques and neurofibrillary tangles (10)*

(12). The drawback of these tangles is that they block the transport system of the neuron, therefore impairing the synaptic communication between neurons (12).

Initially, these alterations such as amyloid plaques and fibrillary tangles begin in the entorhinal cortex and hippocampus of the brain, which affects the individual's memory (5). The locations of these areas of the brain can be seen in *Fig.* 3. The entorhinal cortex functions as a mediator for information that is entering and leaving the hippocampus, where the processes of learning and memory occur (13). Furthermore, other areas of the brain are damaged, causing a detrimental effect on the individual's activities of daily living (ADLs) (5). Although this is the process of Alzheimer's Disease, other forms of dementia also similarly affect an individual.

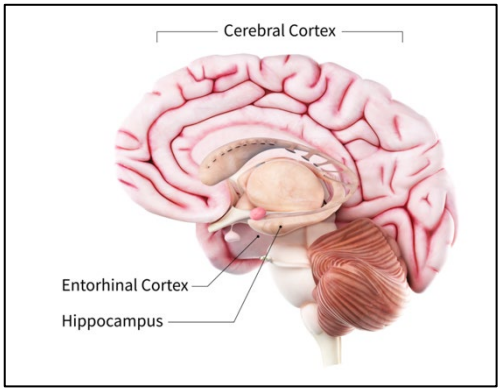

Fig. 3 *Location of the Entorhinal Cortex and Hippocampus in the brain (5)*

There are two forms of AD: early-onset and late-onset. Late-onset Alzheimer's Disease is considered sporadic, and the apolipoprotein E gene (APOE) is seen to be a genetic risk factor, specifically the $\varepsilon 4$ allele of the APOE gene (14,15). The function of APOE is to regulate the amount of cholesterol present (15). Individuals with this allele tend to have amyloid-β onset earlier than those that do not carry the allele (15).

Generally, the greatest risk for an individual having Alzheimer's Disease is their age (4). The one exception to the rule is thousands of individuals living with early-onset Alzheimer's Disease (4). In early-onset Alzheimer's Disease, there are two subtypes: common and genetic (familial) (16). The common type of early-onset AD is very similar in progression to that of late-onset AD, but it forms in adults before the age of 65 (16). The genetic (familial) type of early-onset Alzheimer's Disease is rare, as only a few hundred individuals have this subtype, where a specific gene contributes to their disease (16). The specific gene mutations that are linked to early-onset AD are Amyloid precursor protein (APP), Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2) (16). The pathogenic events that lead to Alzheimer's Disease can be seen in *Fig 4*. On average, individuals will begin showing symptoms between 30-50 years old (16). The risk for both subtypes of early-onset Alzheimer's Disease is a family history (16).

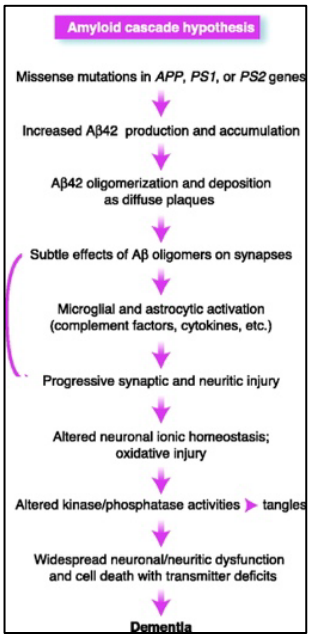

Fig. 4 *Pathogenic events that lead to Alzheimer's Disease (17)*

Symptoms Of Alzheimer's Disease

The signs and symptoms of AD vary based on what stage of the disease the individual is in. A breakdown of the stages of AD can be seen in later sections of this article, however, there are common signs and symptoms that someone with AD may present with. Beginning with noncognitive symptoms, an individual may present with apathy, depression, agitation, aggression, and psychosis (1). The cognitive symptoms of Alzheimer's Disease include problems with language, memory, and thinking (1). In the early stages of the disease, individuals may have difficulties remembering the latest conversations, names of family/friends, and important events, in addition to apathy and depression (1). In the later stages of the disease, individuals may include compromised communication, disorientation, confusion, lack of judgment, changes in behaviors, and difficulty with swallowing, speaking, and walking (1). When symptoms of AD begin, seeing a practitioner is vital so that a diagnosis can be made.

Diagnosis Of Alzheimer's Disease

Diagnosing Alzheimer's Disease varies greatly and is dependent on which stage of the disease the patient currently resides in (10). Individuals on average, live four to eight years following diagnosis (24).

If the patient is in the early stages of the disease, neuropsychological testing, and a Mini-Mental State Examination (MMSE) can help obtain a baseline for testing in the future (10). Checking the thyroid and vitamin B-12 levels are important to identify any secondary causes of dementia and other disorders that are common in the elderly (10). To exclude other forms of dementia, a CT scan and MRI are obtained (10). The most common way to diagnose a patient with Alzheimer's Disease is through neuropathology and the finding of Amyloid- β plaques or neurofibrillary tangles (10).

A Mini-Mental State Examination is a commonly used test of cognitive function among the geriatric population (18). During this assessment, orientation, attention, memory, language, and visual-spatial skills are examined (18). The MMSE's scores range from 0-30 (18). If an individual scores above 26, they are deemed competent, scoring from 19-24 indicates the earlier stages of AD, 10-20 indicates the moderate stage of AD, and scores 9 or less indicate severe AD (19). *Table 1* indicates the scores and matching educational levels (18).

Score	**Educational Levels**
22 or below	7th grade or lower
24 or below	8th grade or some high school
25 or below	High school graduate
26 or below	Some college or high school

Table 1*: MMSE scores and corresponding educational levels (18)*

Treatments

Current treatments for Alzheimer's Disease are donepezil, rivastigmine, galantamine, and memantine and are laid out in *Fig 5* (16,10). These medications work to provide individuals with comfort, dignity, and independence for a longer time (20). The problem with these medications is that the disease is not being modified, rather it is being slowed (20). In 2021, Aducanumab was added to the current treatments for Alzheimer's Disease as a disease-modifying biologic treatment (20). The purpose of this review is to look at three other medications that are in the stage-three process of clinical trials for disease-modifying biologics: gantenerumab, lecanemab, and Solanezumab.

	Donepezil	Galantamine	Rivastigmine	Memantine
Indication	Mild to moderate AD	Mild to moderate AD	Mild to moderate AD	Moderate to severe AD
Mode of action	Selective AChE inhibition	Selective AChE inhibition and allosteric nicotine receptor modulation	Slowly reversible AChE and BuChE inhibition	Non-competitive NMDA-receptor antagonist
CYP450 metabolism	Yes (CYP2D6 and CYP3A4)	Yes (CYP2D6 and CYP3A4)	No, hydrolysed by esterases	No
Half-life	Long (70 h)	Short (7–8 h)	Very short (1 h)	Long (60–100 h)
Doses per day	One	Two (tablets)	Two	Two (first week once a day)
		One (prolonged release capsule)		
Given with food	Irrelevant	Recommended	Yes (increased bio-availability)	Irrelevant
Initial dose	5 mg/day	8 mg/day	3 mg/day (1·5 mg×2)	5 mg/day
Dose escalation	4–6 weeks	Every 4 weeks, up to recommended or tolerated dose	Every 2 weeks, up to recommended or tolerated dose	Every week, up to recommended or tolerated dose
Recommended clinically efficient dose	10 mg/day	16–24 mg/day	6–12 mg/day	20 mg/day

Fig. 5 *Current Treatments for Alzheimer's Disease (10)*

Clinical trials for Alzheimer's disease test and monitor activities of daily living (ADLs), along with other mental examinations, such as a Mini-Mental State Examination determine the effectiveness of a specific drug. Activities of daily living are those skills required to manage one's basic physical needs, including personal hygiene or grooming, dressing, toileting, transferring or ambulating, and eating (21). While progressing through the stages of Alzheimer's Disease and other forms of dementia discussed above, individuals will lose the ability to perform these tasks independently.

History Of Alzheimer's Disease

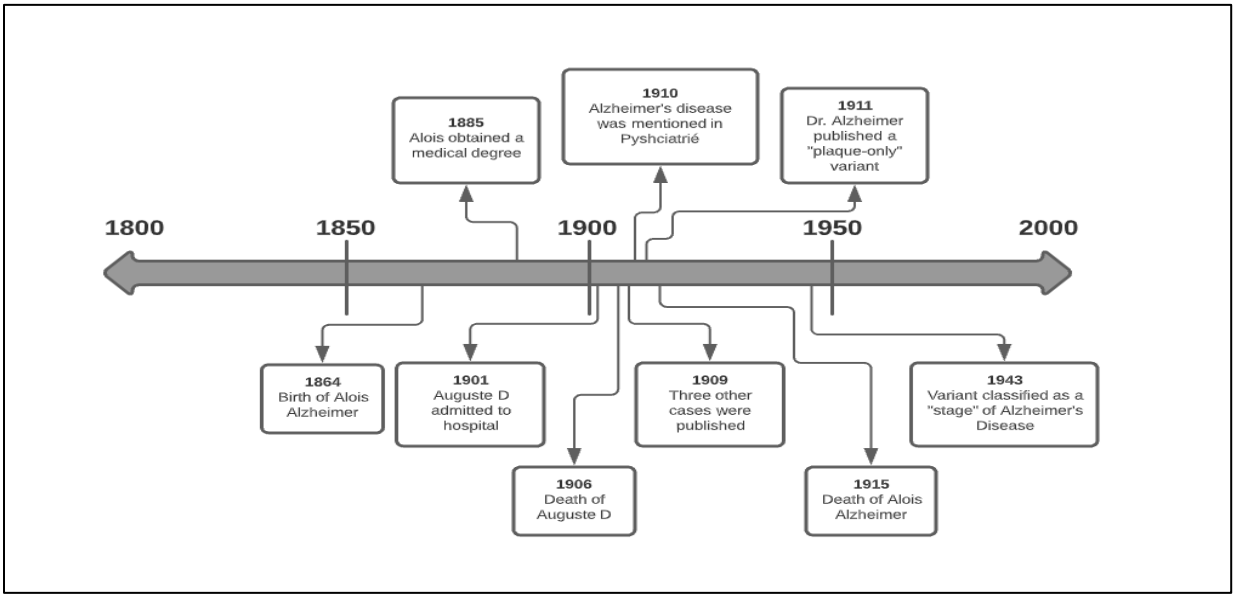

Fig. 6 *The Timeline of the History of Alzheimer's Disease (16,22,6)*

Alois Alzheimer was born (1864) and raised in Marktbreit, Germany (22). Alois attended university in Berlin, Freiburg, and Würzburg where his interest in anatomy and microscopes developed (22). He obtained his degree in medicine from Würzburg with his dissertation focused on anatomy (22). In 1852, Alois applied and accepted a position at the "Community Hospital for Mental and Epileptic Patients in Frankfurt" as a clinical psychiatrist and neuroanatomist (22).

In 1906, Dr. Alois Alzheimer discovered "a peculiar severe disease process of the cerebral cortex" (22). This discovery came after the death of his patient, a 50-year-old woman, Auguste D, whom he first met in 1901 (22). Beginning with her admission to the Frankfurt Psychiatric Hospital on November 25, 1901 (6), her husband commented on a starting symptom of paranoia, which then aggressively progressed into "sleep disorders, disturbances of memory, aggressiveness, crying and progressive confusion" over the next few years until she died in 1906 (22). Proceeding her death and autopsy, Dr. Alzheimer examined Mrs. Auguste's brain at the cellular and tissue level (16). His findings included changes in the brain that included plaques

and “neurofibrillary tangles” (22). With these conclusions, Dr. Alzheimer presented the case and findings at the “37th Meeting of South-West German Psychiatrists in Tubingen,” however there were little to no comments or discussion on the topic (22). Following the meeting, the Tubingen press published and commented on the lectures, however, Dr. Alzheimer’s lecture was only discussed for two lines out of the entire publication (22). This small, yet essential publication began the research and communication on Alzheimer’s Disease (22).

Following Mrs. Auguste’s case, Dr. Alzheimer published three other cases in 1909 (22). In 1910, Alzheimer’s Disease was mentioned in the third edition of the textbook Psychiatrié (22). A year later, Dr. Alzheimer published a “plaque-only variant” where there was no presence of neurofibrillary tangles in Mr. Josef F (22). The difference between the “plaque-only variant” and the presence of both plaque and neurofibrillary tangles was discovered by H-J. Moller and M.B. Graeber as different stages of Alzheimer’s Disease (22).

Only a few years later, in 1915 and at age 51 (22), Dr. Alois Alzheimer died following “renal and respiratory failure” (23).

Stages Of Alzheimer's Disease (24)

Preclinical Stage

At the preclinical stage of Alzheimer's Disease, the individual is not showing any symptoms of the disease, however, their brain is undergoing significant changes (25). Due to not showing symptoms and being high-functional (functioning mentally and physically at a higher level than others with AD (26), individuals are usually not diagnosed in this stage (24).

Mild Stage

Presumably due to aging, individuals at this stage are thought to have mild forgetfulness, but this forgetfulness is thought to come with aging (25). Additionally, they may have problems concentrating on certain tasks, remembering names, recent events, where they put a valuable object, finding correct words to express themselves, plans they made, how to stay organized, managing their money, etc. (25,24). Despite these difficulties, the individual still may work, drive, and participate in social gatherings (27). Due to continuous participation, they may be aware of their memory problems, as well as their friends and family (25). This worry may warrant an exam from a practitioner, who will be able to identify the symptoms and diagnose using specific diagnostic tools (27). Once diagnosed, this is the optimal time to make financial, legal, and end-of-life plans as the individual can participate in these important decisions (27).

Moderate Stage

The moderate stage of Alzheimer's is on average the longest stage, as it may last for several years (27). Patients at this stage have an increasingly more difficult time remembering events, learning new things, planning complex events, and their names, reading, writing, and working with numbers (25). As the disease is progressing, the individual may find difficulty in recognizing family/friends, lose track of time, repeat stories/thoughts/events, and need assistance

with activities of daily living. (25,24). Behavioral changes include moodiness, personality changes, hallucinations, paranoia, delusions, restlessness, agitation, anxiety, and becoming emotional (25). During this time, it is important to find the activities that the individual can still complete independently, those that require simplifying, and finally those activities where assistance is needed (27). A concern in this stage of the disease is wandering from home (23). As the individual progresses through this stage, they may need to transition to a higher level of care (27).

Moderately Severe Stage

During the moderately severe stage, individuals have significant confusion, as seen with not recognizing immediate family members, or thinking that strangers are family members (24). Additionally, they will continue to decline in the ability to perform activities of daily living, and urinary and fecal incontinence begin to occur (24). Finally, the individual has sleep disturbance (24).

Severe Stage

Those in the severe stage begin a decline in health (24). The individual's memory is lost, they need assistance with all ADLs, are unaware of their surroundings, have weight loss, begin declining in their ability to sit, walk, or eat without aid, and have continued problems with incontinence (24).

Very Severe Stage

In the very late stage of the disease, the individual loses the ability to respond to their environment, carry on a conversation, and control movement (27). Conversations are scarce as the individual is only able to say some words and phrases and cannot carry on a conversation (25), this also leads to difficulty in communicating their pain (27). Although interaction and

communication are severely limited in this stage, simple things such as listening to relaxing music, and having gentle care and touch can benefit them (27). A great benefit for individuals suffering from Alzheimer's at the end of their life is hospice care (27). Hospice care functions by providing comfort for the individual, while also keeping their dignity (27) during the last six months or less of their life.

End of Life

During the final stage of Alzheimer's Disease, individuals forget how to swallow (24). This significant problem may cause food/drink to enter the trachea and into the lungs rather than the esophagus to the stomach (24). When food/drink enters the lungs, it may cause infections that the individual is unable to combat (24). Other causes of death to an individual with Alzheimer's Disease are pneumonia, malnutrition, and dehydration (24).

Stage 3 Disease-Modifying Biologic Drugs

Gantenerumab

Gantenerumab is a human anti-amyloid-β IgG2 monoclonal antibody (28). It works by binding to Amyloid-β aggregates such as oligomers, fibrils, and plaques in the brain (28). Gantenerumab is specifically targeted for individuals in the preclinical and mild stages of early-onset Alzheimer's Disease (28). Amyloid plaques are removed by Fc receptor-mediated phagocytosis (28). The current dosage of gantenerumab is 1200 mg/mo. via subcutaneous injection to reduce amyloid plaques (28). There are currently seven clinical trials for gantenerumab, six of which are in stage three trials and can be seen in *Table 2*.

There were four, phase one trials for gantenerumab to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of Gantenerumab (30). The enrollment for these studies was 308 individuals (30,29). In one of the studies, individuals were randomly placed in one of three groups: 60 mg gantenerumab, 200 mg gantenerumab, or placebo (29). The results of this study showed that the level of cortical brain amyloid decreased by 15.6% for those in the 60 mg group and 35.7% for those in the 200 mg group (29). As seen in *Fig. 7*, the amount of amyloid load increases in most parts of the brain in those that were in the placebo group except for the pons, which originally has only a small amount of amyloid deposition (29). With those who were in the 60 mg of gantenerumab, on average, the anterior cingular cortex, medial temporal cortex, and striatum decreased in amyloid deposition, while the other parts of

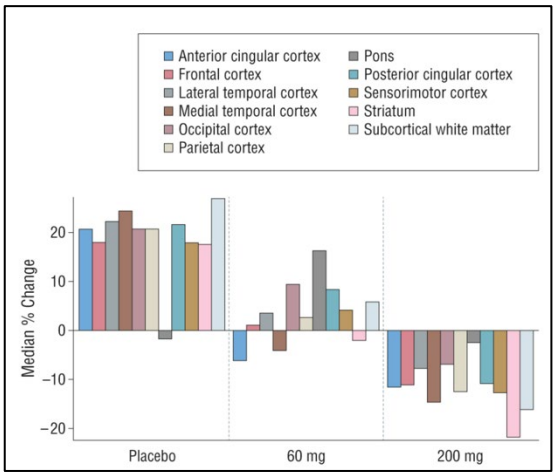

Fig. 6 *Median percent change of amyloid load from baseline of brain areas after treated with placebo, 60 mg of Gantenerumab, and 200 mg of Gantenerumab (29).*

the brain still had an increase in deposition (29). In contrast to the individuals in the placebo and 60 mg of gantenerumab groups, in the 200 mg gantenerumab group, each part of the brain decreased in amyloid load significantly (29). Overall, *Fig. 7* indicates that the individuals in the 200 mg gantenerumab group had the most decrease in amyloid load than the placebo or the 60 mg gantenerumab group.

In the phase two trial, known as the SCarlet RoAD trial, the researchers determined the efficacy and safety of gantenerumab in 797 individuals (30,31). Patients were put into one of three groups: 105 mg gantenerumab, 225 mg gantenerumab, or placebo for two years (31). In December of 2014, the trial was discontinued and unblinded due to futility, however, the results obtained suggested that dosing at higher amounts would be needed (31).

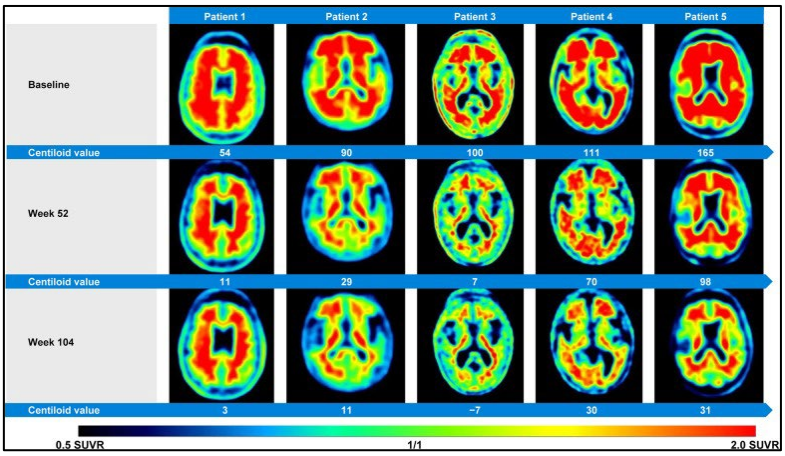

***Fig.** 7 Amount of amyloid-β shown in MRIs of five patients at baseline, week 52, and week 104. (32)*

Following the suggested dose increase of gantenerumab, researchers began a substudy in which 89 patients were placed into a titration group that had a target goal of 1200 mg every four weeks (32). The results of this study were that at the year one check-up, 37% of patients had amyloid-β plaques below the baseline, and in year two, the number increased to 51% (32). *Fig. 8* demonstrates the decrease in amyloid- β plaques at year one (52 weeks) and year two (104 weeks) with PET scan axial images of the brain (32). In conclusion, dosing gantenerumab at 1200 mg for two years gave a strong removal of amyloid-β plaques (32).

In *Table 2* below, current studies of gantenerumab are presented with the start/end dates, active/recruiting stage, the number of participants, and the primary outcomes (8).

Study	Date Started/	Stage	Participants	Primary Outcome(s)

	Projected End date			
"Safety and Efficacy Study of Gantenerumab in Participants with Early Alzheimer's Disease" (33)	August 22, 2018 November 23, 2023	Active	982	Change from baseline to the 116th week in CDR-GS
"A Study to Evaluate the Safety and Tolerability of Long-term Administration of Gantenerumab in Participants with Alzheimer's Disease" (34)	May 22, 2020 April 27, 2023	Active	116	Percentage of participants with adverse and serious adverse events, changes in score of Columbia-Suicide Severity Rating Scale (C-SSRS), participants with Amyloid-Related Imaging Abnormalities-Edema (ARIA-E), participants with Amyloid-Related Imaging Abnormalities-Hemosiderin deposition (ARIA-H), participants with anti-drug antibody (ADA) to Gantenerumab, participants with injection-site reactions, and participants who discontinued treatment
"Efficacy and Safety Study of Gantenerumab in Participants with Early Alzheimer's Disease" (35)	June 6, 2018 November 2, 2023	Recruiting	1016	Change from baseline to 116th week in CDR-GS
"A Study to Evaluate the Efficacy and Safety of Gantenerumab in Participants at Risk for or at the Earliest Stages of Alzheimer's Disease (AD)" (36)	June 24, 2022 October 13, 2028	Recruiting	1200	Change in Preclinical Alzheimer's Cognitive Composite-t (PACC-5) scores from baseline to year four.
"A Study to Evaluate the Safety, Tolerability, and Efficacy of Long-term Gantenerumab Administration in Participants with Alzheimer's Disease" (37)	February 1, 2021 December 27, 2024	Recruiting	2032	Percentage of participants with adverse and serious adverse events, change in C-SSRS, participants with ARIA-E, participants with ARIA-H, and participants with injection-site reactions
"Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease-Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation. Master Protocol DIAN-TU001" (38)	December, 2012 July, 2022	Recruiting	490	Assess cognitive efficacy in individuals whose AD is caused by mutations measured via the DIAN-Multivariate Cognitive Endpoint from a change in baseline to weeks 52, 104, 156, and 208.

Table 2 *Gantenerumab: Stage 3, active or recruiting clinical trials (39).*

Lecanemab

Lecanemab is an IgG_1 monoclonal antibody that targets and binds to soluble aggregated amyloid-β, specifically oligomers and protofibrils (40). This drug was first developed at BioArctic Neuroscience, where they discovered a mutation in the Amyloid Precursor Protein (APP) (41). Individuals with the mutation and Alzheimer's Disease, have high levels of amyloid-β protofibrils and an absence of amyloid plaques (41). There are currently four clinical trials for lecanemab, three of which are in stage three trials: AHEAD 3-45, Clarity AD, and DIAN-TU (42).

The phase one trial's purpose was to determine the safety and tolerability of lecanemab or BAN2401 in 80 subjects with mild-moderate Alzheimer's Disease (43,41). Its methods included varying dosages from 0.1 mg/kg each dose to 10 mg/kg biweekly (43). During this trial, they evaluated Amyloid Related Imaging Abnormalities ((ARIA) E (edema) /H (hemorrhage)) using magnetic resonance imaging (MRI), and the effects on biomarkers by analyzing their Cerebrospinal Fluid (CSF) (43). The results from this trial indicated that the prevalence of ARIA-E/H was no more common than they were in the placebo, the half-life of lecanemab is about seven days, and there were no effects of lecanemab on CSF biomarkers (43). The limitation of this clinical trial was that they could not indicate the most effective dose, because there were no effects on the CSF biomarkers (43). With these specific findings, they moved on to the efficacy of lecanemab in the phase 2b trial (43).

Following the phase one trial, researchers designed a Bayesian adaptive phase 2, proof-of-concept trial (44). The purpose of this trial was to assess the most effective dosage for BAN2401 in individuals with early AD at ≥90% of effect (44). Based on results from the phase

one trial, dosages 5 mg/kg and 10 mg/kg monthly, and 2.5 mg/kg, 5 mg/kg, and 10 mg/kg biweekly were used (44). A simulation of the study was utilized for 800 subjects (44).

In the phase 2b proof-of-concept clinical trial, researchers hypothesized that reducing Amyloid-β aggregates would be an effective way to treat the early stages of Alzheimer's Disease (8). The enrollment for this study was 854 individuals (8). This trial, although it did not meet its original goal of 12-months, as the 10 mg/kg dose showed to be 64% better than the placebo, rather than the target of 80% (8). Additionally, the tolerability of Lecanemab was assessed and there was a 9.9% incidence of ARIA-E/H (8). Overall, at 18-months, analyses showed a reduction in Amyloid-β, while also reducing the clinical decline in various endpoints (8).

Following this phase 2b clinical trial, are the phase 3 Clarity AD, AHEAD 3-45, and DIAN-TU trials as seen in *Table 3* (45).

Study	**Date Started/ Projected End date**	**Stage**	**Participants**	**Primary Outcome(s)**
"AHEAD 3-45 Study: A Study to Evaluate Efficacy and Safety of Treatment With Lecanemab in Participants With Preclinical Alzheimer's Disease and Elevated Amyloid and Also in Participants With Early Preclinical Alzheimer's Disease and Intermediate Amyloid" (46)	July 13, 2020 October 25, 2027	Recruiting	1400	A45 – change from baseline in PACC5 (Preclinical Alzheimer Cognitive Composite 5) score at 216 weeks A3 – change from baseline in Amyloid Positron Emission Tomography (PET) Standard Uptake Value Ratio (SUVr) at 216 weeks
"A Study to Confirm Safety and Efficacy of Lecanemab in Participants With Early Alzheimer's Disease (Clarity AD)" (47)	March 27, 2019 August 29, 2024	Active	1766 (set)	Baseline change in the CDR-SB at 18 months
Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease-Modifying Treatments in Individuals With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation (DIAN-TU)" (48)	December 22, 2021 October, 2027	Recruiting	168	Week 24-104 and week 24-208 in tau PET in the population with symptoms

Table 3 *Lecanemab: Stage 3, active or recruiting clinical trials (45)*

Solanezumab

Solanezumab is also a humanized form of immunoglobulin G1 monoclonal antibody that works by binding to the mid-domain of the amyloid-β peptide (7). This antibody is designed to promote increased clearance of amyloid-β peptides (7). Specifically, Solanezumab works by removing soluble Amyloid-β that is toxic to neuronal synapse function (49).

The purpose of the phase one trial was to assess the pharmacodynamics, pharmacokinetics, safety, and tolerability of Solanezumab between white and Japanese individuals with AD (50). The individuals were divided into two groups: white and Japanese, then further divided and given via intravenous infusion either 0.5 mg/kg, 1.5 mg/kg, 4.0 mg/kg, or 10.0 mg/kg of Solanezumab (50). Additionally, a study was done in Japan where 400mg of Solanezumab was given to 33 individuals with mild-moderate AD, and the time intervals were varied between one, four, or eight weeks (49). Biomarkers studies found specific changes in "plasma and CSF Aβ40, Aβ42, plasma pyro-Glu Aβ, and plasma and CSF N-terminally truncated Aβ, but not CSF total tau and phosphorylated tau" (49).

In the phase two trial, the purpose was to assess Solanezumab's safety and tolerability (49). The enrollment for this trial was 52 patients, and they were divided into two groups (Placebo and Solanezumab), then further subdivided into four groups: 100mg every 4 weeks, 100mg once weekly, 400 mg every 4 weeks, and 400 mg once weekly (51). Those in the Solanezumab group received the drug for 12 weeks (51). To determine the effectiveness of Solanezumab, researchers used magnetic resonance imaging and CSF (51). For patients in the group taking 400 mg once weekly, Solanezumab decreased the amount of unbound Aβ(1-40) in CSF, however, the treatment increased the amount of unbound Aβ(1-42) in CSF (51). In

conclusion, researchers believe that Solanezumab may be able to mobilize Aβ(1-42) from plaques of amyloid-β (51).

EXPEDITION 1 and EXPEDITION 2 led researchers into phase 3 trials (52). The purpose of these studies was to see changes from baseline to the 80th week on the Alzheimer's Disease Assessment Scale, specifically the 11-item cognitive subscale (ADAS-cog11) and the Alzheimer's Disease Cooperative Study, the Activities of Daily Living scale (ADCS-ADL) (52). In EXPEDITION 1, 1012 patients were enrolled, and in EXPEDITION 2 1040 patients were enrolled (52). In each study, patients were randomly assigned into two groups: placebo or Solanezumab (52). Those in the Solanezumab group received the dose at 400mg intravenously every 4 weeks for 18 months (52). The results in EXPEDITION 1 showed -0.8 points on the ADAS-cog11, and -0.4 points on the ADCS-ADL score as seen in *Table 4* (52). Following EXPEDITION 1, EXPEDITION 2, showed -1.3 points on the ADAS-cog11, and +1.6 points on the ADCS-ADL as seen in *Table 5* (52). As seen in the primary outcomes of EXPEDITION 1 and EXPEDITION 2, no study showed noteworthy progress (52).

Variable	Mean Change from Baseline to Wk 80 (95% CI)		Mean Difference (95% CI)	P Value
	Placebo	Solanezumab		
ADAS-cog11 score†	4.5 (3.3 to 5.8)	3.8 (2.5 to 5.0)	−0.8 (−2.1 to 0.5)	0.24
ADAS-cog14 score‡	5.8 (4.3 to 7.3)	4.5 (2.9 to 6.0)	−1.4 (−2.9 to 0.2)	0.09
ADCS-ADL score†	−8.7 (−10.4 to −7.0)	−9.1 (−10.9 to −7.4)	−0.4 (−2.3 to 1.4)	0.64
CDR-SB score§	1.8 (1.3 to 2.3)	2.0 (1.5 to 2.4)	0.1 (−0.3 to 0.6)	0.51
NPI score¶	0.6 (−1.5 to 2.6)	−0.3 (−2.4 to 1.7)	−0.9 (−2.6 to 0.8)	0.29
MMSE score	−2.0 (−2.8 to −1.2)	−1.4 (−2.2 to −0.6)	0.6 (0.0 to 1.2)	0.06
Free Aβ_{40} in CSF — pg/ml	80.9 (−2100.5 to 2262.3)	−1127.3 (−3272.4 to 1017.9)	−1208.2 (−2132.4 to −283.9)	0.01
Free Aβ_{42} in CSF — pg/ml	−28.5 (−160.0 to 102.9)	−54.4 (−186.7 to 77.9)	−25.8 (−88.3 to 36.6)	0.41
Total Aβ_{40} in CSF — pg/ml	−1902.1 (−6660.1 to 2855.8)	1325.4 (−3162.0 to 5812.9)	3227.6 (1253.6 to 5201.5)	0.002
Total Aβ_{42} in CSF — pg/ml	−242.3 (−1144.4 to 659.7)	471.4 (−436.0 to 1378.8)	713.7 (309.1 to 1118.4)	<0.001

Table 4 *EXPEDITION 1: Primary and Secondary Outcomes (52)*

Variable	Mean Change from Baseline to Wk 80 (95% CI)		Mean Difference (95% CI)	P Value
	Placebo	Solanezumab		
ADAS-cog11 score†	6.6 (5.2 to 7.9)	5.3 (4.0 to 6.7)	−1.3 (−2.5 to 0.3)	0.06
ADAS-cog14 score†	7.5 (5.8 to 9.1)	5.9 (4.3 to 7.5)	−1.6 (−3.1 to 0.1)	0.04
ADCS-ADL score†	−10.9 (−12.7 to −9.1)	−9.3 (−11.2 to −7.5)	1.6 (−0.2 to 3.3)	0.08
CDR-SB score	1.9 (1.4 to 2.4)	1.6 (1.2 to 2.1)	−0.3 (−0.7 to 0.2)	0.17
NPI score	3.0 (0.8 to 5.1)	2.8 (0.7 to 5.0)	−0.2 (−1.8 to 1.5)	0.85
MMSE score	−2.8 (−3.6 to −2.0)	−2.1 (−2.8 to −1.3)	0.8 (0.2 to 1.4)	0.01
Free $A\beta_{40}$ in CSF — pg/ml	−649.0 (−2139.5 to 841.5)	−1258.1 (−2695.8 to 179.7)	−609.1 (−1228.4 to 10.2)	0.05
Free $A\beta_{42}$ in CSF — pg/ml	−35.1 (−129.5 to 59.3)	1.0 (−94.1 to 96.2)	36.1 (−1.0 to 73.3)	0.06
Total $A\beta_{40}$ in CSF — pg/ml	−876.4 (−4342.5 to 2589.8)	2156.8 (−1211.9 to 5525.4)	3033.1 (1628.4 to 4437.9)	<0.001
Total $A\beta_{42}$ in CSF — pg/ml	323.8 (86.2 to 561.5)	726.6 (489.4 to 963.9)	402.8 (307.7 to 497.8)	<0.001

Table 5 *EXPEDITION 2: Primary and Secondary Outcomes (52).*

The third phase three trial, EXPEDITION 3, was completed due to the first two, phase three trials being unsuccessful (7). The trial design for EXPEDITION 3 explicitly stated that the patients with AD must have evidence via biomarker of an amyloid-related disease through a positron-emission tomography (PET) scan or cerebrospinal fluid (CSF) (7). The enrollment of the EXPEDITION 3 study was 2129 individuals with AD, 1057 individuals received the Solanezumab treatment, and 1072 received the placebo (53). Solanezumab was administered for 76 weeks via intravenous infusion at 400mg or the placebo every four weeks (7). To determine the effectiveness of Solanezumab, they assessed based on the ADAS-cog14, a similar scale to that of ADAS-cog11 used in the EXPEDITION 1 and EXPEDITION 2 trials (7). The results from the primary outcome as seen in *Table 6* showed the mean change at 80 weeks was +6.65, whereas the placebo change at 80 weeks was +7.55 (7). The differences in the primary and secondary outcomes indicated overall that Solanezumab did not significantly reduce cognitive decline (7).

Outcome	Raw Score at Baseline		Raw Score at 80 Wk		Least-Squares Mean Change at 80 Wk		Estimated Difference at 80 Wk (95% CI)	P Value†
	Placebo	Solanezumab	Placebo	Solanezumab	Placebo	Solanezumab		
Primary outcome: ADAS-cog14 score	29.70±8.50	28.87±8.26	36.11±14.27	35.09±13.28	7.44±0.36	6.65±0.36	−0.80 (−1.73 to 0.14)	0.10
Secondary outcomes								
MMSE score	22.62±2.89	22.81±2.77	19.09±5.56	19.62±5.30	−3.66±0.16	−3.17±0.15	0.49 (0.10 to 0.88)	—
ADCS-iADL score	45.37±8.14	45.60±7.93	39.01±11.86	39.83±11.41	−7.17±0.32	−6.17±0.32	1.00 (0.17 to 1.83)	—
ADCS-ADL score‡	66.69±9.15	67.02±8.67	59.00±14.61	60.20±13.52	−8.77±0.39	−7.42±0.39	1.35 (0.33 to 2.37)	—
FAQ score	10.60±7.11	10.31±6.81	15.73±8.10	15.35±8.24	5.57±0.21	5.17±0.21	−0.40 (−0.93 to 0.13)	—
CDR-SB score	3.93±1.95	3.88±1.90	6.02±3.38	5.72±3.18	2.21±0.11	1.87±0.10	−0.34 (−0.57 to −0.11)	—
iADRS score§	105.70±13.95	106.73±13.47	93.04±23.71	94.81±22.15	−14.59±0.54	−12.92±0.53	1.68 (0.29 to 3.06)	—

Table 6 *EXPEDITION 3 Primary Outcomes (53)*

There are currently two clinical trials for Solanezumab, DIAN-TU, and A4 as seen in *Table 7*. DIAN-TU (Dominantly Inherited Alzheimer Network Trial) is a study of potential treatments for individuals who are at risk or have early-onset Alzheimer's Disease that is caused by a genetic mutation (53). Particularly, assessing the safety, tolerability, biomarkers, and cognitive efficacy of Solanezumab (53). This drug will be administered intravenous infusion at increasing doses every four weeks (53). Alternatively, the purpose of A4 (Clinical Trial for Solanezumab for Older individuals who may be at risk for Memory Loss) is to test whether Solanezumab can slow the progression of memory difficulties that are associated with amyloid-β plaques (54). This drug will be administered through an intravenous infusion at 400-1600mg every four weeks for 240 weeks (54).

Study	Date Started/ Projected End date	Stage	Participants	Primary Outcome(s)
"Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease-Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation. Master Protocol DIAN-TU001" (53)	December, 2012 July, 2022	Recruiting	490	"Assess cognitive efficacy in individuals with mutations causing dominantly inherited AD as measured by the change from baseline in the DIAN-Multivariate Cognitive Endpoint"
"Clinical Trial of Solanezumab for Older Individuals Who May Be at Risk for Memory Loss (A4)" (54)	February 28, 2014 June 30, 2022	Active	1150	"Change from baseline of the Preclinical Alzheimer Cognitive Composite (PACC)"

Table 7 *Solanezumab: Stage 3, active or recruiting clinical trials (55)*

Conclusion

Dr. Alois Alzheimer, a German neuroanatomist and clinician discovered Amyloid-β plaques and neurofibrillary tangles following the death of Auguste D in 1906. Following this discovery and research in years to follow, Alzheimer's Disease was founded as a degenerative brain disease caused by cell damage. Alzheimer's Disease currently affects six million Americans, and it is expected to increase to 13 million by 2050. The stages of AD vary based on the resource, however, this paper focused on six stages: preclinical, mild, moderate, moderately severe, severe, and very severe with the longest stage being moderate. As the progression through each stage increases, the independence of performing an individual's activities of daily living decreases. The effects of AD on the brain and activities of daily living are known, however treating AD is another story. The current treatments for AD are only used to slow the progression and treat the symptoms rather than change the disease state. Aducanumab, the first disease-modifying biologic drug was approved for use in 2021. Three drugs, gantenerumab, lecanemab, and Solanezumab are also disease-modifying biologics and are currently in stage-three clinical trials. Ganterumab showed promising results in phases one and two, and currently has six, phase three trials in progress. Lecanemab did not show promising results in its phase one trial, as researchers could not determine the most effective dosing. The phase two trial, however, showed a reduction in Amyloid-β while also reducing the decline in several clinical endpoints. Lecanemab currently has three, phase three trials in progress. Solanezumab in both phase one and multiple phase two trials did not show promising results, however, they continue researching as there are two, stage three trials in progress. In conclusion, the research for Alzheimer's Disease has a promising outlook, especially with the disease-modifying biologic drugs currently in clinical trials.

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