Bloomberg Intelligence BI

Alzheimer's Outlook

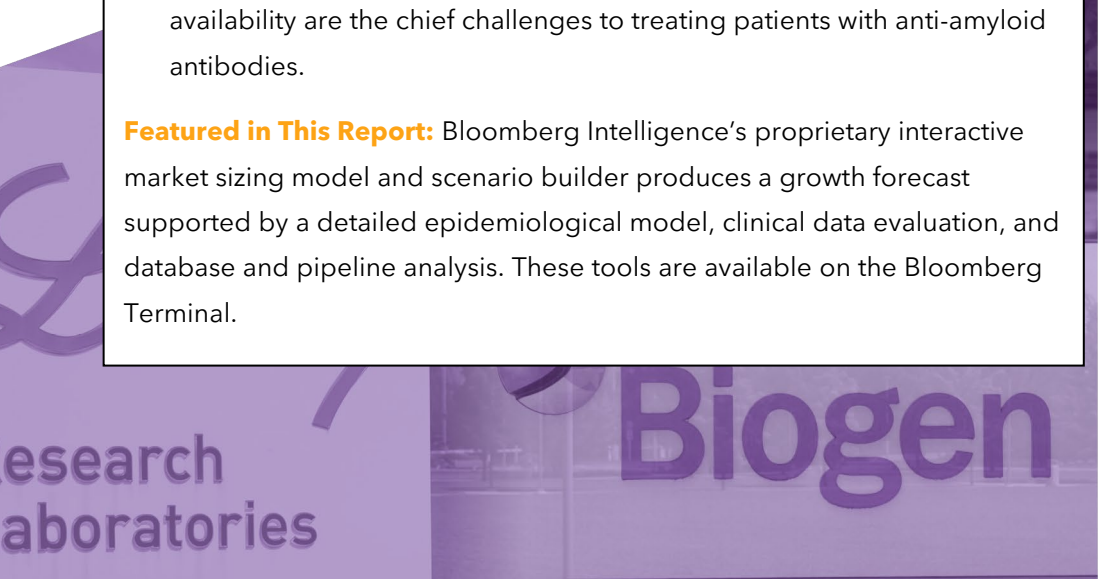
2024

Market Heads to $13 Billion, With Significant Opportunity For Novel Treatments

Biogen and **Eisai**'s Leqembi and **Eli Lilly**'s donanemab are set to face off in the market for treatments that slow the course of Alzheimer's disease, which our risk-adjusted analysis finds can surge to $13 billion by 2030 from $250 million this year. The lack of a cure leaves substantial room for new methods from **Roche**, **AbbVie**, **Alector**, **Prothena**, **Novo Nordisk** and others.

- **Stiff Competition:** Global sales of just anti-amyloid antibodies – the drug types furthest along in development – could be about $10 billion by 2030, with Leqembi accounting for $3.2 billion and Lilly's donanemab and remternetug, $6.5 billion.
- **Early Treatment Is Next Frontier:** The next goal is to treat patients before symptoms appear, a global population estimated at more than 155 million – more than three times that of people who exhibit signs of Alzheimer's dementia.
- **Obstacles to Growth:** Cost, insurance coverage and neurologist availability are the chief challenges to treating patients with anti-amyloid antibodies.

Featured in This Report: Bloomberg Intelligence's proprietary interactive market sizing model and scenario builder produces a growth forecast supported by a detailed epidemiological model, clinical data evaluation, and database and pipeline analysis. These tools are available on the Bloomberg Terminal.



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More detailed analysis and interactive graphics are available on the Bloomberg Terminal

Section 1. Executive Summary

$13 Billion
Projected sales of disease-modifying drugs by 2030, from $250 million in 2024

$760 Billion
Minimum estimated US health and long-term care costs by 2040

>155 Million
Estimate of global presymptomatic Alzheimer's patients

Dynamics Shift in $13 Billion Market With Room to Grow

Alzheimer's disease is among the world's most pressing health care challenges, affecting more than 6.9 million people in the US and 40 million globally – numbers that are expected to double by 2040. Health and long-term care costs by then are likely to exceed $760 billion in the US.

Our analysis indicates that the market for so-called disease-modifying therapies – as opposed to those that treat just symptoms – can jump to $13 billion by 2030 from $250 million this year. Further growth is possible from drugs attacking earlier stages of the disease, with more than 155 million people worldwide believed to have preclinical Alzheimer's. Given the unmet need and the lack of a cure, there's ample room for drugmakers including Roche, AbbVie, Alector, Prothena and Novo Nordisk.

Key Research Topics

- **Leadership to Change:** Biogen and Eisai's Leqembi, approved in 2023, may generate $3.2 billion in 2030 sales. But its first-to-market advantage could be short-lived as Lilly's donanemab will likely get cleared this year. The Lilly treatment, plus its self-injected formulation, could fuel $6.5 billion in sales. Both anti-amyloid antibody drugs were tested in patients with early Alzheimer's, representing a population of 10 million in the US.
- **Seeking Advantage in Dosing:** Lilly's drug relies on infusions every four weeks, while Biogen and Eisai's needs infusions every two, though monthly dosing might be approved this year. The companies are developing self-injected versions, which would ease administration, increase patient adherence and boost sales.
- **Expanding Through Off-Label:** Almost 50% of physicians in a BI survey would consider off-label use of anti-amyloid antibodies for patients with preclinical or moderate to severe dementia, adding upside to our global sales estimates.
- **Attacking Disease Early:** Treating presymptomatic patients based on blood tests is the next goal. An estimated global population above 155 million – three times that of people who show signs of Alzheimer's dementia. Biogen, Eisai and Eli Lilly have drugs in that pipeline.
- **Launch Hurdles**: Creating treatment centers will be key to access and, with patient data collected by Medicare, will help determine what drug leads the market. Cost, insurance coverage and neurologist availability are central challenges to anti-amyloid treatment.

Companies Impacted

Since it has the only disease-modifying treatment, the Biogen-Eisai partnership leads Alzheimer's drug sales. Consensus sees Leqembi accounting for 0.9% of Biogen's total revenue this year. By 2030, that increases to 19%, which we think will be difficult unless it gains momentum after a sluggish launch. Analysts estimate that donanemab will make up 0.1% of Lilly's total 2024 revenue, increasing to 5% by 2030. For small-cap biotechs like Alector, Cassava and AC Immune, approval could be critical to company survival.

Section 2. Catalysts to Watch

Regulatory Reviews to Get More Attention Than Trials

Though more than 20 clinical data readouts on Alzheimer's drugs are expected this year, the more significant catalysts will be likely US and EU decisions on approving Lilly's donanemab, the first competitor to Biogen and Eisai's Leqembi (lecanemab). Biogen and Eisai are also expected to apply for a subcutaneous, self-injected formulation of their drug using a pen-type device. And if the partnership's pending application is cleared for monthly maintenance intravenous infusions, it could minimize donanemab's potential edge in dosing.

Critical Milestones

- **2Q24**: EU advisory committee opinion on Biogen-Eisai's lecanemab
- **June 10, 2024:** US advisory committee to discuss safety, efficacy and dosing of Lilly's donanemab and vote on recommendation to FDA
- **2Q-3Q24**: EU advisory committee opinion on donanemab
- **3Q24:** Biogen-Eisai to submit for approval of subcutaneous formulation of lecanemab for monthly self-administered dosing
- **3Q24**: Data on Alzheon's valiltramiprosate for early to mild Alzheimer's
- **2H24:** Possible EU approval of Leqembi
- **2H24:** Possible US approval of monthly maintenance dosing of lecanemab
- **2H24:** Possible EU, Japan approvals of donanemab
- **Late 2024**: Possible EU approval of Anavex's blarcamesine for early Alzheimer's
- **Late 2024:** Trial data on Cassava's simufilam in mild to moderate disease
- **2025**: Primary readout on Lilly's subcutaneous remternetug in early disease
- **2H25:** Primary readouts of trials for Novo Nordisk's semaglutide
- **2027:** Completion of donanemab prevention study in preclinical Alzheimer's
- **2029:** Completion of lecanemab prevention study in preclinical disease

Section 3. Disease Overview

Leading Cause of Dementia Affects Women More Heavily

Alzheimer's disease is the most common cause of dementia, affecting more than 6.9 million people in the US. It's also a leading cause of death, with mortality increasing 140% from 2000 to 2021 while deaths from HIV and stroke decreased. The estimated lifetime risk for Alzheimer's dementia increases with age. And the disease disproportionately affects women: Almost a quarter of those 65 or older are expected to develop Alzheimer's, compared with 12% for men.

3.1 US Health, Long-Term Costs to Top $760 Billion by 2040

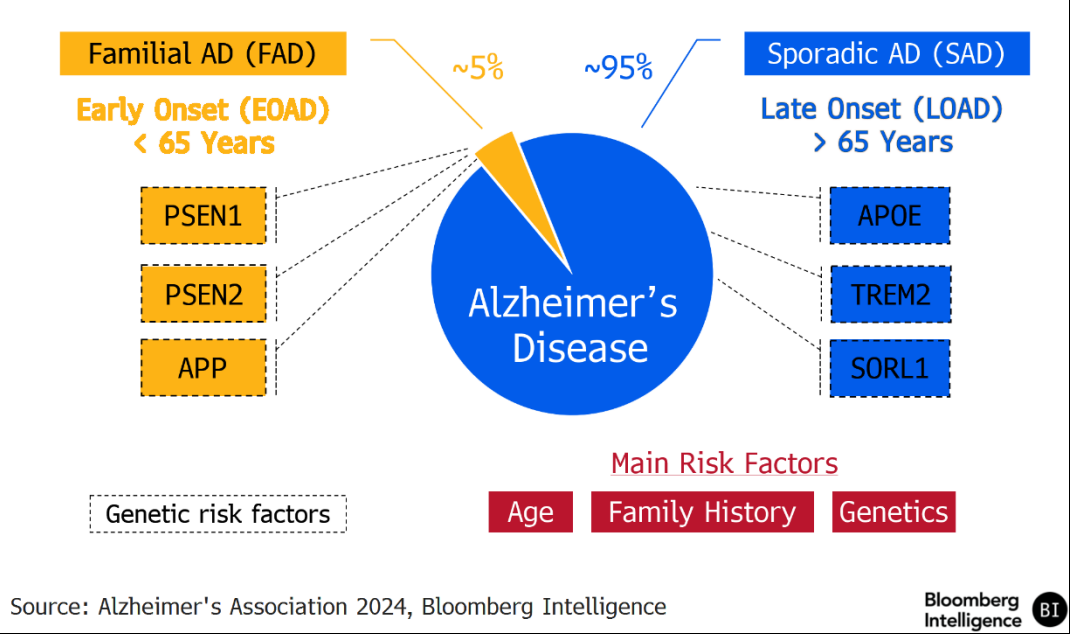
Combined health and long-term care costs for Alzheimer's are expected to exceed $360 billion this year in the US – including $232 billion in Medicare and Medicaid and $91 billion in out-of-pocket expenses. They're likely to top $760 billion in 2040.

Alzheimer's is progressive, characterized by amyloid deposits in the brain and tau neurofibrillary tangles within neurons, leading to continued loss of memory and cognitive function. Its complexity means Alzheimer's molecular drivers aren't completely understood, preventing consensus on the mechanism that has the highest potential as a disease-modifying treatment.

Genetic variants play substantial roles in the disease's development. Rare and highly penetrant mutations in the APP, PSEN1 and PSEN2 genes drive autosomal-dominant Alzheimer's, typically with early disease onset (see Figure 1). Common gene pairs of late-onset sporadic Alzheimer's (the APOE, TREM2 and SORL1 genes) have small individual causal effects that when combined contribute to genetic liability for disease.

BI **Alzheimer's symptoms nearly always appear after age 65.**

Figure 1: Alzheimer's Subtypes, Risk Factors



As the US population ages, increased rates of chronic diseases like Alzheimer's will have profound implications for the health-care system and societal costs. Nearly three in 10 Americans will be 65 or older in 2100, with death rates exceeding birth by 2038. Today, people over 55 make up 56% of total health spending but only 30% of the population. Demographic trends suggest that the increasing number of elderly and retired people and shrinking numbers of working-age individuals is a long-term trend that may result in far-reaching societal changes.

3.2 Eisai, Biogen Develop First Disease-Modifying Treatment

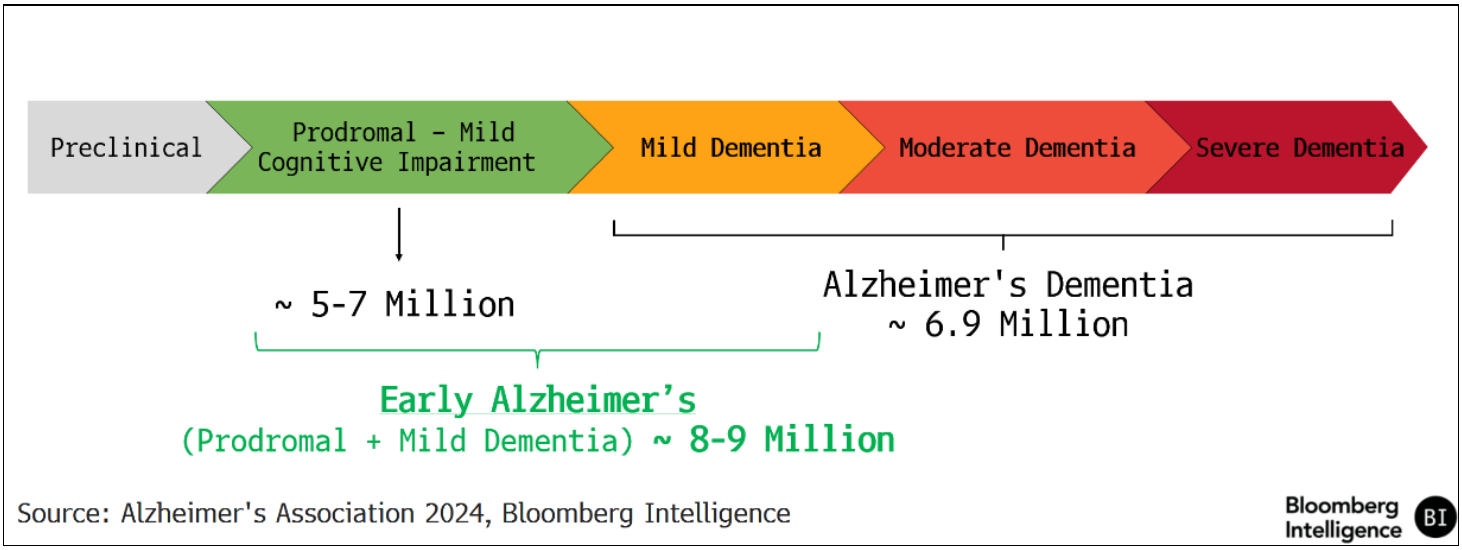
Alzheimer's therapy primarily involves treating symptoms, for which there are six approved medications. And though symptomatic drugs can't prevent Alzheimer's progression, controlling how severely conditions worsen still is beneficial.

Eisai and Biogen's amyloid-lowering Leqembi in 2023 became the first disease-modifying therapy to receive full FDA approval. Several others are in advanced stages of clinical development or regulatory review, most notably Lilly's amyloid antibody donanemab, which could be approved by year-end.

Accurate patient categorization in Alzheimer's is needed to best identify individuals who could benefit from treatment, particularly as disease-modifying therapies emerge. Brain imaging, genetic screening, accounting for patient demographics and lifestyle, conducting cognitive and functional assessments, and confirming whether the Alzheimer's pathology is amyloid- and/or tau-based will provide the most comprehensive view to inform patient-tailored treatment. Such methods can also identify who is at particular risk of adverse events.

Biomarker use has increased over the years, with blood-based markers on the horizon. That will be an important step away from expensive PET imaging for amyloid and tau quantification, and invasive spinal taps for cerebrospinal fluid analysis.

Figure 2: Alzheimer's Disease Stratification



Section 4. Mechanistic Summary

Anti-Amyloids Unlock New Generation of Treatment

For decades, Alzheimer's treatment consisted of temporarily easing just some symptoms. That changed with Biogen and Eisai's Leqembi (lecanemab), which used anti-amyloid antibodies to slow the course of the disease. Lilly is likely to gain approval for its anti-amyloid therapy this year. But such treatments are far from functional cures, leaving opportunities for novel mechanisms that target neuroinflammation, neurotransmitter dysfunction and synaptic plasticity. Roche, AbbVie, GSK, Biogen and Novo Nordisk are among the drugmakers exploring such possibilities.

4.1 Moving Beyond the Amyloid-Reduction Hypothesis

For the past two decades, most Alzheimer's clinical trials have focused on drugs that target amyloid deposits in the brain, yielding more than 200 trial failures and causing many experts to question the validity of the hypothesis. But recent results for lecanemab and Lilly's donanemab affirmed amyloids' central role and that reducing the peptide's deposits slowed disease progression and cognitive decline over 18 months. It's clear, however, that amyloid reduction alone isn't enough to halt or cure the disease.

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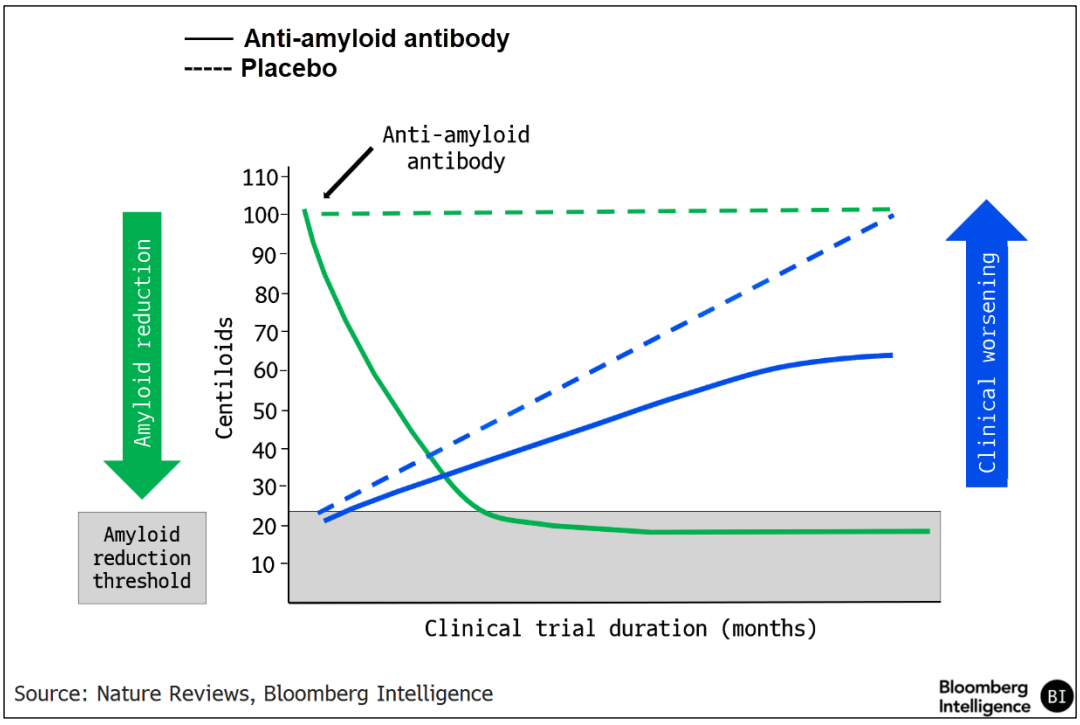
The pace that cognitive function worsens is tempered by reducing amyloid deposits.

Figure 3: Amyloid Reduction vs. Cognitive Decline



Given the modest impact of anti-amyloid antibodies on cognition, approaches that combine treatments or use biomarkers could better address difference among patients. The research framework characterizes individuals based on biomarker evidence of amyloid, tau and

neurodegeneration pathology – providing a comprehensive view that could be employed for profiling an individual's risk and optimizing treatment.

Abundant research points to a significant role for p-tau in the disease's development and progression, but conflicting preclinical and clinical data make it difficult to confirm the hypothesis. Tau plays critical roles in stabilizing neurons, allowing them to function properly. But when the protein is hyperphosphorylated – a biological process believed to occur downstream of amyloid-beta production – it tends to collect inside neurons by forming neurofibrillary tangles, leading to cell death. The result is progressive dysfunction of cognitive, motor and psychological abilities.

Subgroup analysis of Lilly's Trailblazer-ALZ 2 study of donanemab showed that patients with lower levels of p-tau217, about a third of trial participants, had a 46% slowing in disease progression, compared with 26% for those with high levels.

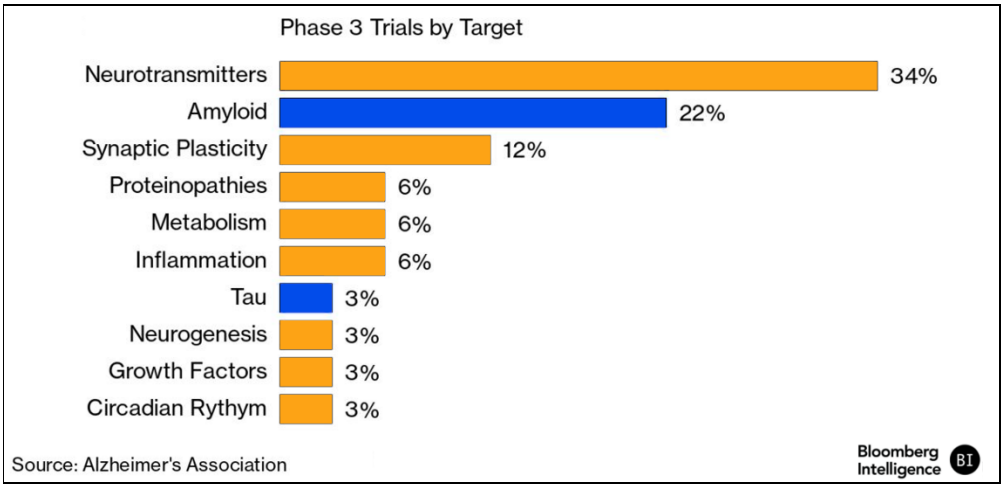
Various mechanisms targeting tau are in the late-stage pipeline, including Biogen and Ionis Pharmaceuticals' antisense oligonucleotide BIIB080, Johnson & Johnson's p-tau antibody JNJ 63733657 and Lilly's O-GlcNAcase inhibitor.

4.2 Personalized Approaches to Treatment Are Critical

Genetic studies indicate a heterogeneous disease mechanism, but most studies aren't designed to capture Alzheimer's complex drivers. Multiple pathological – and not yet fully understood – processes result in amyloid and tau accumulation, neuroinflammation and neurotransmitter dysregulation, making personalized approaches and multiple target interventions crucial.

Strategies aimed at reducing neuroinflammation directly include AbbVie and Alector's TREM-2 antibody AL 002, Tiziana Life Sciences' CD3 intranasal antibody foralumab and Novartis' IL-1b inhibitor canakinumab. Novo Nordisk GLP-1 agonist semaglutide and Cerecin's ketone body stimulant tricaprilin could indirectly affect neuroinflammation through metabolic mechanisms. Other strategies include using a shingles vaccine to confer protection against Alzheimer's dementia. Based on retrospective data, GSK is interested in exploring the use of its shingles vaccine to prevent dementia onset, though the mechanisms remain unknown.

Figure 4: Diverse Approaches Reflect Complex Causes



Section 5. Efficacy Summary

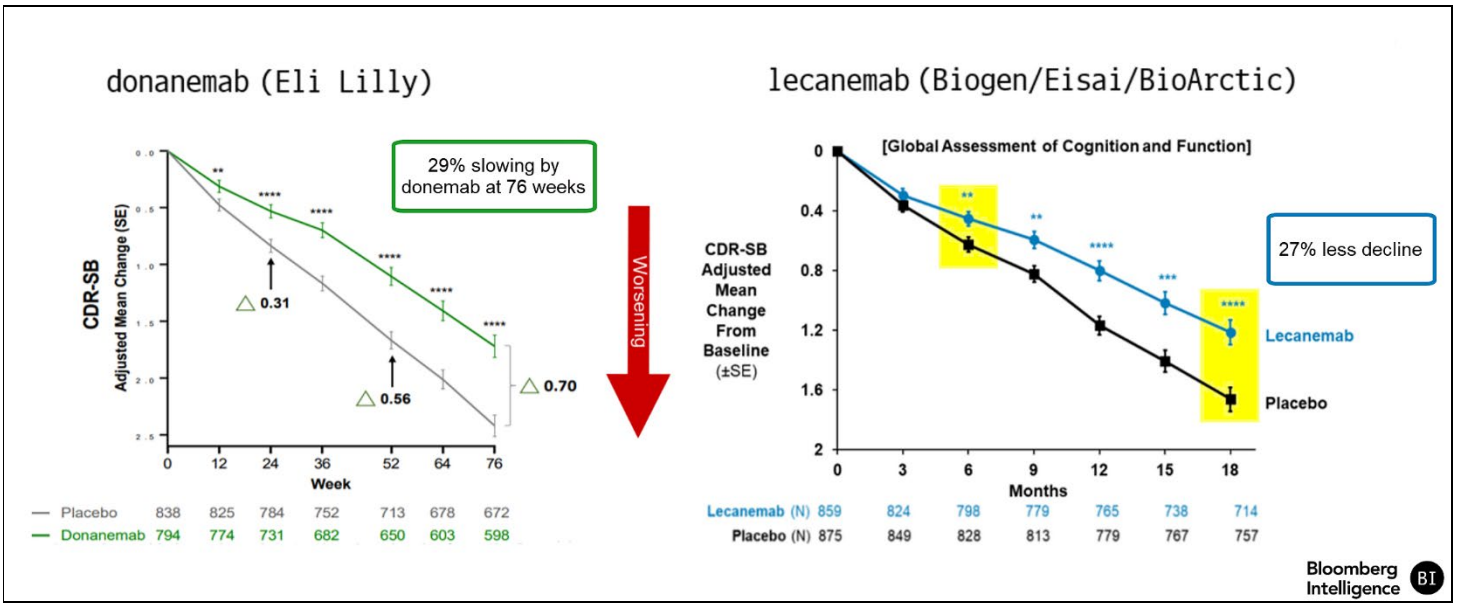
Amyloids Don't Capture Alzheimer's Heterogeneity

Anti-amyloid antibodies, like Biogen and Eisai's Leqembi, could reshape the Alzheimer's treatment landscape. But though its modest slowing of cognitive decline is a step in the right direction, it is far from a functional cure. Pursuing mechanisms that go beyond amyloids is paramount to developing comprehensive treatment strategies, allowing physicians to match the right therapy to the appropriate population.

5.1 Differences Among Drugs, Between Men and Women

Reducing brain amyloid levels slows cognitive decline but Alzheimer's still progresses. Lilly's donanemab prompted disease progression to slow 29% at 18 months in the TrailBlazer-Alz-2 trial, compared with 27% for Biogen and Eisai's Leqembi in the Clarity AD trial, even though donanemab patients had more severe disease (Figure 5). Donanemab showed a statistically significant difference as early as three months – which wasn't seen with Leqembi – and 66% of patients stopped taking the drug at one year since Lilly's trial design required ceasing treatment after achieving amyloid negativity thresholds. Despite that, disease slowing continued.

Figure 5: Cross-Trial Comparison of Amyloid Antibodies



Source: Bloomberg Intelligence

Subgroup analysis of the Clarity AD trial suggests that may not benefit from treatment as much as men. Leqembi delayed cognitive decline by 43% for men and just 12% for women. Similar trends were observed in Biogen and Eisai's aducanumab trials, and we await a detailed subgroup analysis of donanemab to better assess if the discrepancy is drug-specific or peculiar to a drug class.

Since the trials weren't powered to evaluate individual subgroups, real-world data from Medicare registries should help shed light on potential sex differences, which could lead to greater scrutiny during patient screening.

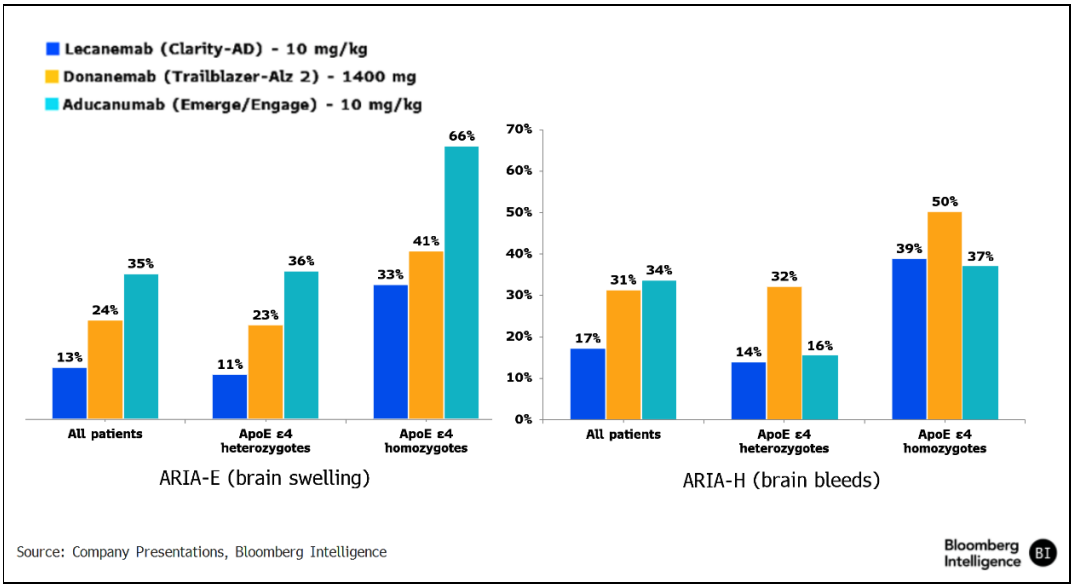
5.2 Bleeding, Swelling Side Effects in Brain Can Be Fatal

Amyloid-related imaging abnormalities, which can be lethal, are the most common side effect of amyloid antibodies. ARIA have two categories: ARIA-E for edema (brain swelling) and ARIA-H, for hemorrhage (brain bleeding). Although the cause remains under investigation, it is thought to be driven by increased vascular permeability following an inflammatory response, leading to the leakage of blood products. ARIA can only be diagnosed with an MRI scan, making it essential for radiologists to recognize and monitor the condition – a difficult feat given the small lesion sizes.

While most ARIA are asymptomatic, some patients can develop headaches, confusion, nausea, dizziness, seizures and, rarely, death.

BI **Amyloid-related abnormalities like brain swelling or bleeding can be a lethal side effect of amyloid antibodies.**

Figure 6: Common Amyloid Imaging Abnormalities



The pace of amyloid removal could affect the rate of adverse events, particularly ARIA. Lilly's donanemab showed faster amyloid clearance than Biogen and Eisai's Leqembi but the rate of ARIA was similar. Roche's trontinemab reached amyloid clearance in just 12 weeks, with no ARIA reported at the interim analysis. That suggests that the speed and depth of amyloid removal likely isn't driving ARIA.

ARIA remain poorly understood and it's too soon to conclude that the risk is directly related to the speed of amyloid removal rather than the way the plaques are removed, particularly from vascular amyloid complexes.

5.3 Longer-Term Leqembi, Rivals Show Encouraging Results

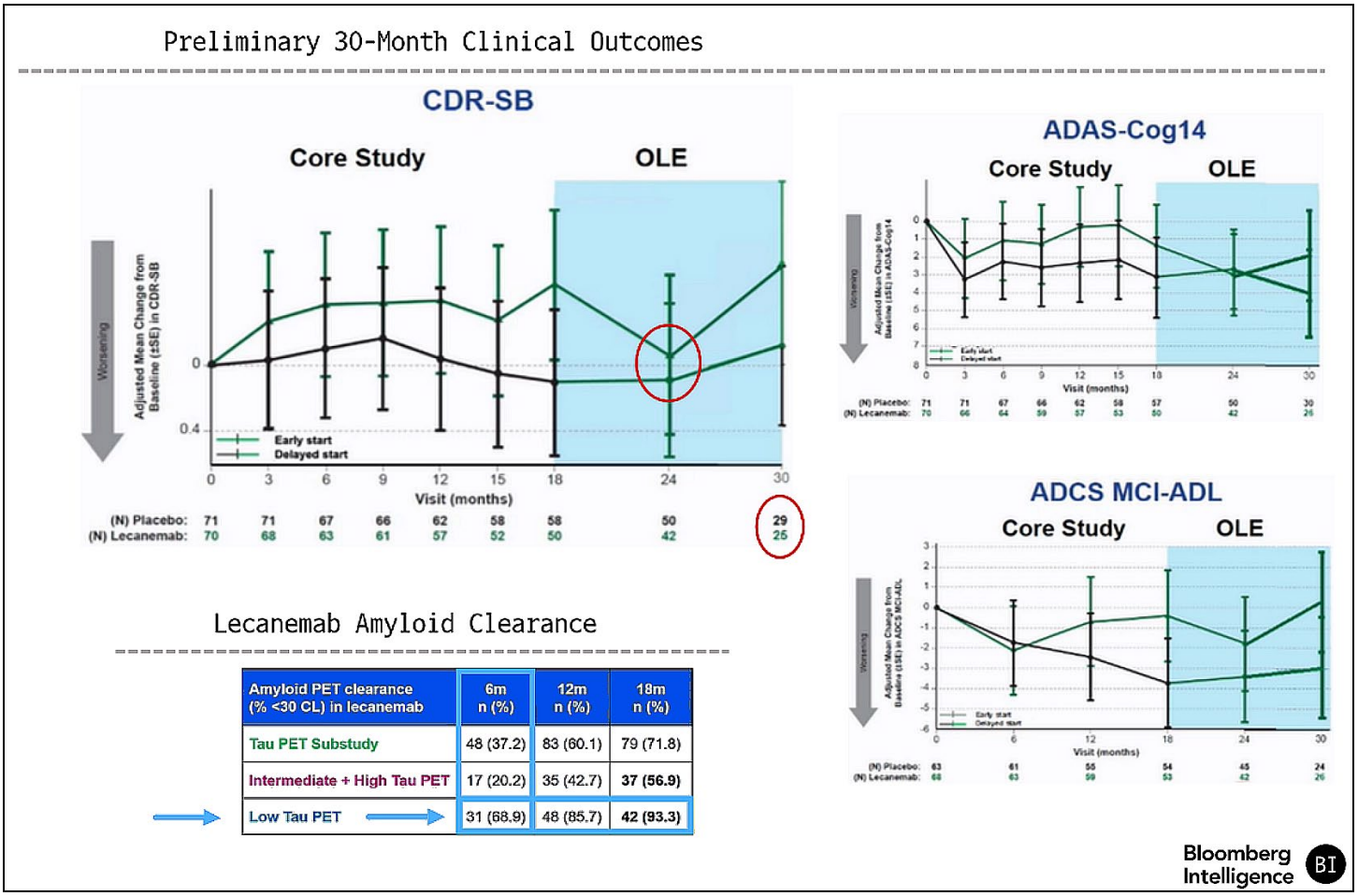
Biogen and Eisai presented additional findings from the open-label extension of its Clarity AD trial, with early data on patients treated for 24 months intravenously. The OLE phase suggested that Leqembi may continue to slow cognitive decline beyond 18 months, however that is difficult to assess given the lack of placebo comparison. Both “early” and “delayed” start groups continued to progress, but that could improve, assuming a constant rate of slowing decline and making follow-up key.

Differences between treatment and placebo across clinical endpoints increased during the first 18 months, but subsequently narrowed with the initiation of Leqembi in the core placebo group from 18 to 24 months. That could hint at a potential disease-modifying effect, but more data are needed.

Additional subgroup analysis from the OLE of Clarity AD highlighted early data on the low-tau population treated for 30 months intravenously. The OLE phase suggested that the lecanemab-treated low-tau subgroup surprisingly didn't demonstrate a clear benefit. Neither did patients who switched to lecanemab from a placebo in months 24-30 (while 69% of low-tau patients achieved amyloid clearance below 30 centiloids in the first six months of Clarity AD), though that, too, is difficult to assess given the lack of a placebo comparison. Similar trends were observed in secondary cognitive and functional measurements.

After a dip at 24 months, both early and delayed start groups hinted at a potential improvement, but longer follow-up and data from more patients are needed.

Figure 7: Patients With Low Tau May Not Benefit More



Amyloid PET clearance (% <30 CL) in lecanemab	6m n (%)	12m n (%)	18m n (%)
Tau PET Substudy	48 (37.2)	83 (60.1)	79 (71.8)
Intermediate + High Tau PET	17 (20.2)	35 (42.7)	**37 (56.9)**
Low Tau PET	31 (68.9)	48 (85.7)	**42 (93.3)**

Source: AD/PD 2024, Bloomberg Intelligence

Early data on Biogen and Eisai's subcutaneous anti-amyloid antibody lecanemab, presented at the 2023 Clinical Trials on Alzheimer's Disease conference in Boston, showed a comparable pharmacokinetic profile to the approved intravenous drug and removed amyloid at similar rates. An increase in imaging abnormalities seen in drug-naive patients treated with subcutaneous lecanemab bears watching, with brain inflammation (ARIA-E) observed in 17% and small brain bleeds (ARIA-H) in 22%. Regulatory filing was delayed to the third quarter from the first to meet an FDA request for longer-term immunogenicity data, but increased adverse events may pose additional hurdles.

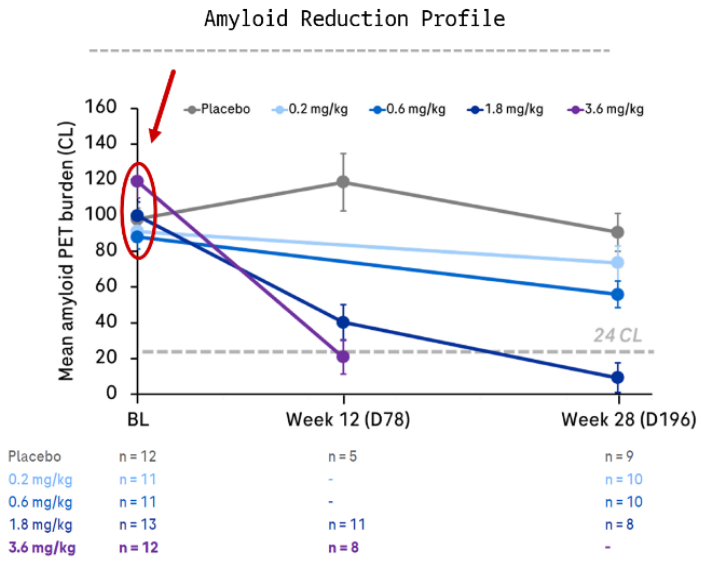
Lilly could follow with its self-injected subcutaneous treatment remternetug, with early Phase 1 data highlighting a similar safety profile as subcutaneous lecanemab, but that isn't expected to launch until 2026.

Roche presented updated Phase 1b/2a data on its novel brain-shuttle antibody targeting amyloid-beta trontinemab, with the active transport component aimed at facilitating brain penetration. Additional results at the 2024 Alzheimer's Disease and Parkinson's Disease Conference showed robust amyloid removal at the highest dose tested (3.6 mg/kg), as measured by amyloid PET

imaging. Though the sample sizes were small, it's encouraging that by week 12, 63% of participants (five of eight) achieved an amyloid-negativity threshold (below 24.1 centiloids).

Safety data are encouraging, with no ARIA incidence in patients treated at the highest dose. Improved safety and rapid amyloid clearance could carve out a spot for trontinemab in an increasingly crowded anti-amyloid field.

Figure 8: Highest Dose Removes Amyloid Quickly With No ARIA



Safety Profile: MRI Findings

12-week interim analysis

Total number of participants with at least one AE , (%)	Cohort 4 3.6 mg/kg or Pbo (n = 15)
Infusion related reaction (IRR)[2]	7 (46.7%)
Anemia[3]	1 (6.7%)

Total number of participants with event [events per participant], (%)	Cohort 4 3.6 mg/kg or Pbo (n = 14)
ARIA-E[4]	0
ARIA-H[5]	
Microhemorrhage	0
Leptomeningeal hemosiderosis (LH)	0
ARIA-E with concurrent ARIA-H	0
Macrohemorrhage	0

Source: AD/PD 2024, Bloomberg Intelligence

Lilly presented additional data from its Trailblazer-Alz 2 study of donanemab at the Clinical Trials on Alzheimer's Disease conference, highlighting significant amyloid reduction regardless of APOE-e4 status. Distinct amyloid-clearance dynamics were observed, with noncarriers achieving greater and faster removal of amyloid plaques than homozygous carriers. That latter group saw a slower removal that seemed to plateau at about 50% reduction.

Efficacy in the low-medium tau population was similar across genotypes, though trends suggest that noncarriers could have a greater benefit. That needs to be confirmed with larger studies, as differences in baseline demographics, sample size, dose interruptions and fewer overall homozygous patients in the trial make it difficult to reach a conclusion.

5.4 Amyloid, Tau Vaccines Emerge as Viable Approaches

Grifols' Araclon Biotech unit reported final data from the Phase 2 study of ABvac40, an active vaccine against AB40, in patients with early Alzheimer's disease. Results pointed to a 38% reduction in cognitive decline on the MMSE scale. Crossover extension indicated robust responses in patients that received a booster – eliciting maximum antibody levels up to four times greater than during initial dosing – while placebo crossover patients showed a similar magnitude in immunogenicity as patients treated in Part A. No ARIA-E was observed, and

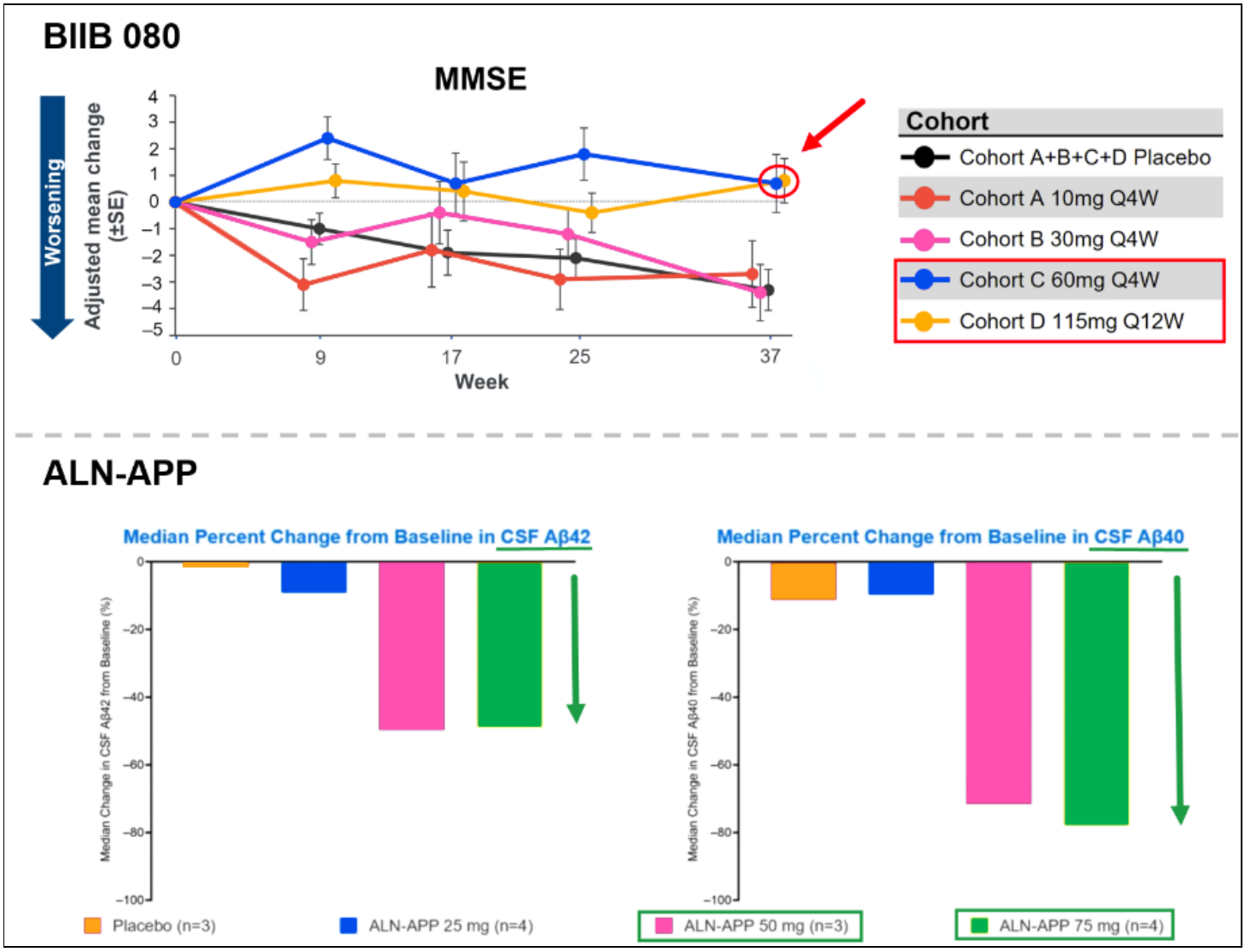
patients that received a booster in Part B had no ARIA. The study wasn't powered for cognitive endpoints, however, and larger trials are needed.

AC Immune presented early data on its anti-Abeta liposomal vaccine ACI-24.060, showing similar binding affinity as anti-amyloid antibodies. Phosphorylated-tau vaccine candidate ACI-35.030 offered evidence of target engagement as measured by robust anti-p-tau antibody titers in the cerebrospinal fluid of treated patients.

Biogen, working with Ionis, presented cognitive measures from the Phase 1b study of BIIB080, a microtubule-associated protein tau-targeting antisense oligonucleotide designed to reduce tau protein production. Previous data presented at the Alzheimer's Disease and Parkinson's Disease Conference confirmed target engagement, and an early look at cognitive effects hinted at modest efficacy.

Interim results from Alnylam Pharmaceuticals and Regeneron Pharmaceuticals' ALN-APP, an RNA interference compound targeting amyloid precursor protein, showed significant reductions in APP alpha and beta – primary soluble components of amyloid deposits – in cerebral spinal fluid samples. That was sustained up to 10 months after a single intrathecal (spinal) infusion.

Figure 9: Early Results of RNA-Modulating Approaches



Source: CTAD 2023, Bloomberg Intelligence

Alzheon presented two-year follow-up results from its Phase 2 biomarker study of oral drug ALZ-801 in APOE4 carriers with Alzheimer's disease. Results showed that plasma P-tau 181 levels were reduced from week 13 and maintained up to week 104. Memory scores measured by the RAVLT survey showed stabilization over 24 months, while imaging results showed slowed atrophying in the hippocampus – a brain region involved in memory formation and recall. ALZ-801's safety profile showed no increased risk of ARIA-E or ARIA-H. A long-term extension study at three and four years starting soon should help build the case for potential approval, as could Phase 3 trial data expected late this year.

Roche's gamma secretase modulator RG6289 showed promising early biomarker results that demonstrated a dose-dependent response, yielding an increase in nontoxic amyloid species AB37 and AB38 and a decrease in toxic AB40 and AB42 in young and elderly healthy volunteers. The company reported a favorable safety profile, but we have yet to see detailed safety results. RG6289 is entering an 18-month Phase 2 study, GABriella, in patients with prodromal Alzheimer's

disease, with recruitment expected to begin in the first half. The trial will focus on safety, tolerability and the effects of RG6289 on Alzheimer's-related biomarkers. After trial failures with gamma secretase inhibitors, there's renewed hope that modulating this key enzyme could lead to a safe decrease in toxic amyloid species.

Priavoid's PRI-002 (contraloid), an orally available, anti-prionic D-peptide drug that targets amyloid oligomers and protofibrils, showed a promising safety profile in healthy elderly volunteers. Its small size allows it to cross the blood-brain barrier, and it doesn't interfere with the formation or clearance of nontoxic amyloid monomer species. The drug's manageable safety profile is encouraging, and early efficacy measured via the CERAD word list after only 28 days of daily drug exposure bodes well.

The proof-of-concept Phase 2 study, the PRImus-AD trial, is recruiting patients in Europe, with initial results expected in the fourth quarter of 2025.

Novo Nordisk is running two Phase 3 trials in Alzheimer's disease using the GLP-1 analog oral semaglutide, based on anecdotal evidence, ranging from its own trials to real-world data. Though there's always a risk of failure with trials based on anecdotal evidence, there's a robust body of preclinical data that show effects across several aspects of the disease. In particular, the positive impact of GLP-1 analogs on vascular health could have some beneficial effects in dementia, especially cases involving brain blood vessels. Novo's decision to include patients with small-vessel disease in the Evoke Plus trial is a good sign.

Multiple tyrosine kinase inhibitors — classically used in oncology — are being studied in Alzheimer's. TKIs are thought to act in the brain by switching the neuroimmune system from a toxic state to a protective one. Phase 3 data showed that AB Science's low-dose masitinib (4.5 mg/kg) led to a slight decrease in cognitive decline (ADAS-Cog) and minimal improvement in daily life function (ADAS-ADL), while high-dose masitinib (6.5 mg/kg) failed to replicate such findings. A Phase 2 study of Novartis' nilotinib led to a modest lowering of amyloid and p-tau in cerebralspinal fluid but had no impact on slowing of cognitive or functional decline. The results require confirmation in larger, well-designed Phase 3 studies — with an emphasis on screening for and quantifying amyloid and tau levels during patient selection.

5.5 Tau Levels, Synaptic Plasticity Hold Promise

The specific role of tau in Alzheimer's is uncertain, but it remains a compelling therapeutic target in light of preclinical evidence suggesting that lowering tau may slow cognitive decline. Early data from Biogen and Ionis' antisense oligonucleotide BIIB 080 (intrathecal) demonstrated a dose-dependent mean reduction in cerebralspinal fluid P-tau levels of 50% observed at 24 weeks. Eisai's anti-tau antibody E2814 (intravenous) demonstrated a 40% reduction in CSF MTBR-tau-243 (tau tangle biomarker) at 12 weeks.

Although early, the results showed a greater reduction in tau biomarkers when compared to semorinemab, Roche's anti-tau antibody, which achieved a 20% reduction in P-tau yet failed to show consistent benefits on cognition. That signals that Eisai's drug may achieve tau reduction thresholds needed for a clinical benefit to emerge.

Impaired synaptic plasticity and neuronal loss in excitatory synapses are early events in Alzheimer's disease and are thought to directly affect learning and memory. Although these phenomena are poorly understood, multiple studies that target the imbalance in cellular and molecular mechanisms of synaptic plasticity in Alzheimer's are underway. Fujifilm Toyoma Chemical's endonerpic targets sigma-1 receptors, which are thought to modulate microglial function, while AgeneBio's levetiracetam aims to suppress abnormal neural activity. Athira Pharma's fosgonimeton stimulates neuronal growth factors with the goal of promoting the formation of new neuronal connections, or synapses.

These early studies show nominal changes in cognition and disease-relevant biomarkers, requiring further validation in larger randomized studies.

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Fujifilm Toyoma and AgeneBio are developing drugs aimed to address impaired synapses, a characteristic of early Alzheimer's.

Figure 10: Cross-Trial Comparison of Synaptic Modulators

	endonerpic Fujifilm Toyoma		levetiracetam AgeneBio	
Dose	224 mg	448 mg	125 mg	
Dosing frequency	1x daily		1x daily	
Route of administration	Oral		Oral	
Stage of Development	Phase 2		Phase 2	
Study duration	52 weeks		4 weeks	
Patients enrolled	159	154	17	17
Baseline characteristics			Group A	Group B
MMSE, mean	18.2	18.4	24.5	22.6
CSF P-tau 181, mean	102.6	95.0	N/A	N/A
CSF AB42, mean	417.8	439.1	N/A	N/A
Efficacy Overview				
Change from Baseline				
ADAS-Cog 11	-0.47	-0.84	0.0	-2.5
ADAS-ADL	0.23	1.29	0.3	-0.3
CSF P-tau 181, mean	-3.94	-7.30	N/A	N/A
CSF AB42, mean	-9.70	11.55	N/A	N/A

Bloomberg Intelligence BI

Source: JAMA, Bloomberg Intelligence

Genetic analyses of Alzheimer's and robust epidemiological data have sparked renewed interest in immune responses as potentially causal components. It is thought that a vicious cycle of neuropathology and pro-inflammatory glial activation leads to excessive neurodegeneration as the blood-brain barrier integrity is compromised. Early neuroimmune modulator results from Longeveron's Lomocel-B weren't impressive. Vaccine approaches offer more promise, with robust immune responses against amyloid peptides and favorable safety profiles. Vaxxinity's UB311 had no cognitive benefits, while Araclon's ABvac40 led to a 18% slowing of decline.

Potential safety, efficacy and logistical advantages of a vaccines over monoclonal antibodies support the development of this next generation of anti-amyloid therapies.

Section 6. Global Market Model

Biogen-Eisai Team, Lilly to Dominate $13 Billion Market

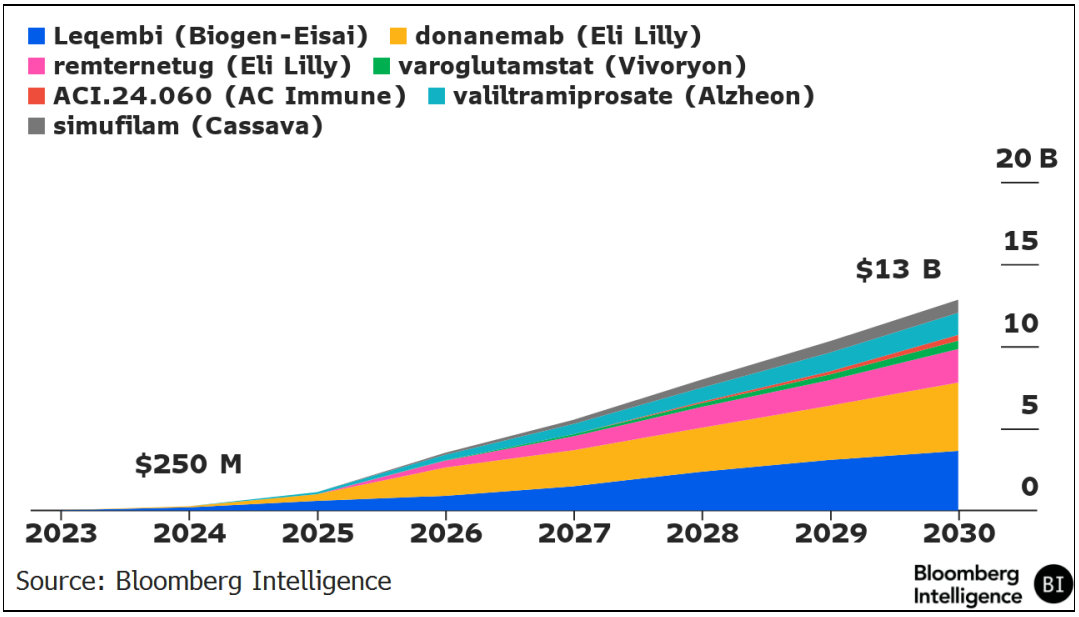
The global market for Alzheimer's could top $13 billion by 2030, according to our risk-adjusted analysis (Figure 11). The first treatments – from a Biogen-Eisai partnership and, likely this year, Lilly – could account for almost $6.5 billion of the total.

6.1 Lilly Rival to Biogen Drug Likely to Get 2024 Approval

Biogen and Eisai in July received full approval for their amyloid-reducing antibody Leqembi and will likely dominate Alzheimer's drug sales this year, given their first-to-market advantage. But Lilly is hard on their heels, with an FDA decision for its amyloid antibody donanemab expected by year-end. Leqembi sales have been slow, with our analysis projecting $250 million combined in 2024 if donanemab is approved – 16% above consensus. The total could increase by decade's end to $10 billion including donanemab's self-injected formulation, remternetug. Sales would be much higher if the companies succeed in moving their drugs to asymptomatic patients – a far larger population.

Novel mechanisms in the late-stage pipeline from several drugmakers could add another $3 billion in sales by 2030.

Figure 11: BI Sales Scenario ($)



Leqembi is one of Biogen's few shots at much-needed near-term revenue growth, but the drug's sales have been sluggish. Our risk-adjusted scenario analysis sees sales at 26% below consensus for 2030. The launch was delayed by logistical hurdles and safety concerns, reining in expectations. Consensus for 2025 is 60% lower than it was at the time of FDA's accelerated

approval in 2023 and more cuts could be needed. Estimates imply just a 0.9% contribution to Biogen's bottom line this year, though that's expected to climb to 19% by 2030.

Lilly's donanemab is likely to launch by the end of 2024, and elements of its dosing regimen look better than Leqembi's.

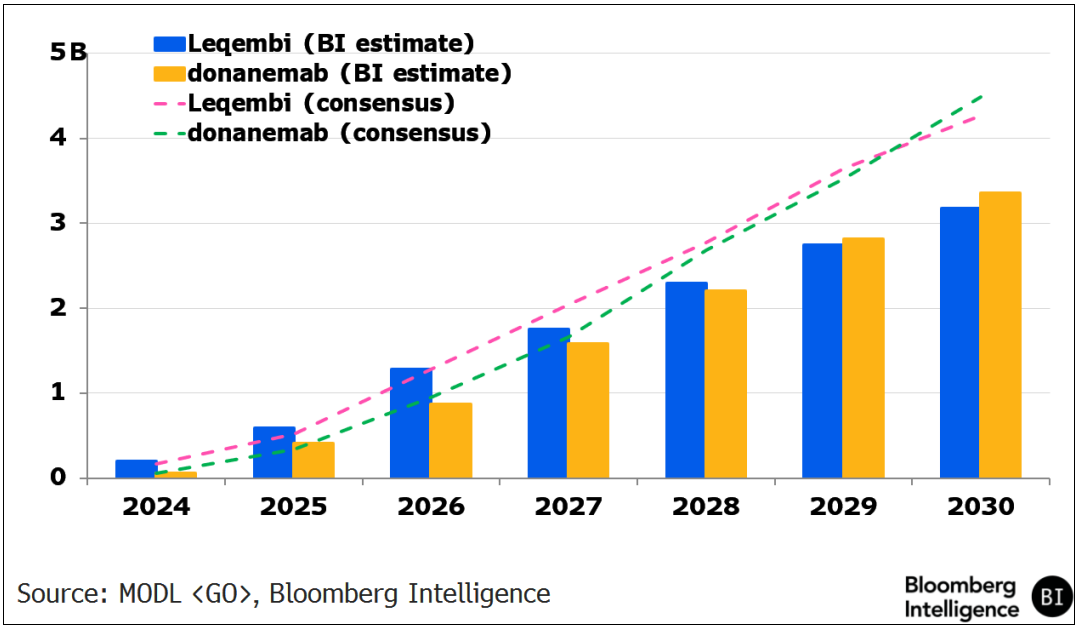
Significant obstacles to diagnosing and prescribing Leqembi have led to a slower ramp-up than expected, missing the drugmakers' goal of treating 10,000 patients by the end of the first quarter. Regulatory delays for maintenance dosing (monthly vs. biweekly) of the self-injected, subcutaneous formulation will likely compound the launch woes. If approved, sales of donanemab could exceed Leqembi's in 12 months, in part due to more convenient dosing and because patients can stop receiving the drug once amyloid levels reach a clearance threshold.

We project $405 million in donanemab sales for 2025 (20% above consensus) and $580 million (11% above) for Leqembi.

BI

Donanemab sales are expected to exceed Leqembi's by 2029.

Figure 12: Sales Projections ($)

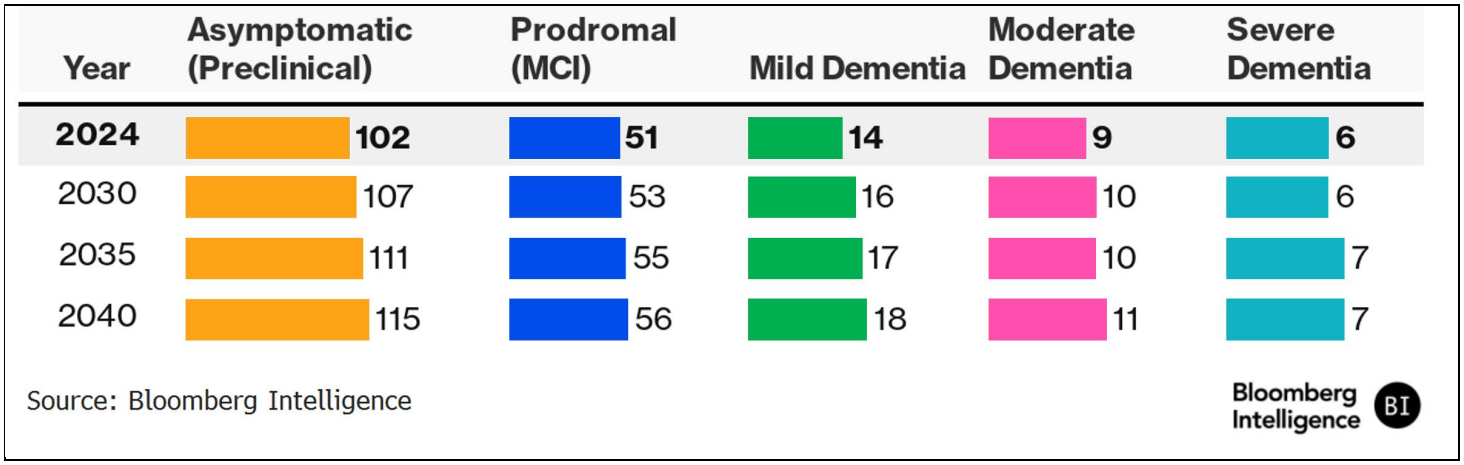


6.2 Asymptomatic Treatment Offers Biggest Opportunity

Our epidemiology starting point is total Alzheimer's incidence in the US, Europe, China and Japan. Focus then turns to early stages – that is, mild cognitive impairment (prodromal) and mild dementia due to the disease – representing 73% of the total Alzheimer's population. Among the increasing number of genetic risk factors identified, the apolipoprotein E gene remains the strongest and most common. More than half of Alzheimer's patients carry one copy of the APOE-e4 allele, doubling or tripling the risk of developing the disease. People with two copies have as much as a 15-fold risk.

Most drugs in development are aimed at treating early Alzheimer's, though asymptomatic or preclinical stages represent a much larger opportunity – exceeding the global MCI and Alzheimer's population by about 17 million.

Figure 13: Alzheimer's Patients in US, EU, China, Japan (Millions)



Section 7. Pipeline Overview

Regulatory Review to Overshadow Trial Results in 2024

An FDA decision on Lilly's donanemab and a filing by Biogen and Eisai on self-injected subcutaneous lecanemab this year, both delayed from the first quarter, will be the biggest milestones in Alzheimer's therapy this year. More than 20 reports from clinical trials on various drugs are due as well.

7.1 Clinical Readouts Expected on Several Novel Mechanisms

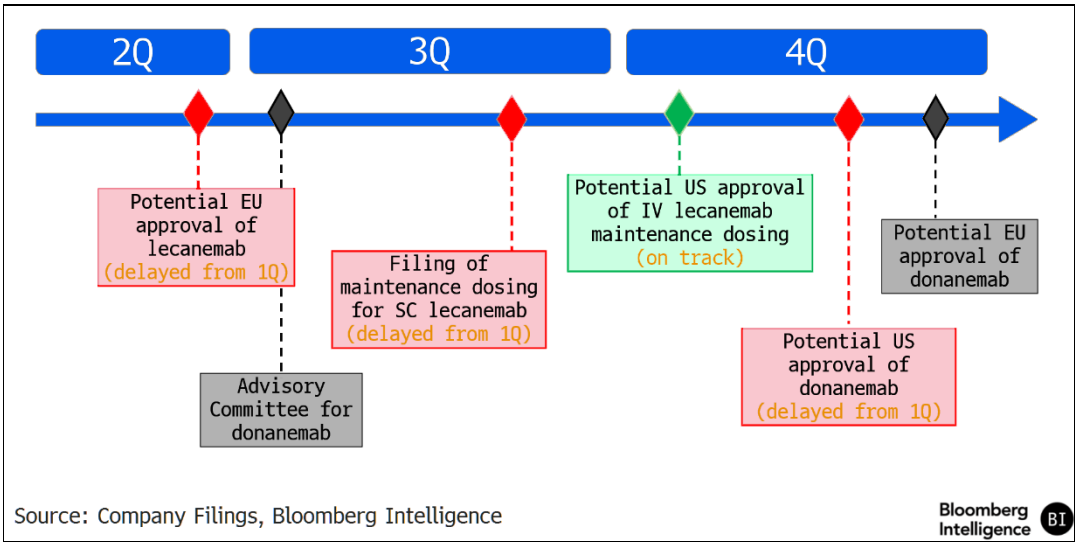
The most significant Alzheimer's catalyst for 2024 would be an FDA decision on Lilly's donanemab, the first potential competitor to Biogen and Eisai's Leqembi. Review by an FDA advisory committee was requested just days before the agency's expected decision date — unusually tight timing. An ad comm also was held before full approval of Leqembi, highlighting the increased scrutiny for this novel class of drugs. The EU may clear donanemab this year as well.

Biogen and Eisai hit regulatory delays, with their application for the subcutaneous formulation of lecanemab pushed until the third quarter. A filing for monthly maintenance intravenous infusions of lecanemab was submitted in March and if approved could minimize donanemab's edge for dosing.

BI

This could be a pivotal year for regulatory decisions on the current leading Alzheimer's drugs.

Figure 14: Key Regulatory Catalysts in 2024



Early- and late-stage data for novel mechanisms are emerging for various approaches, including vaccines, small molecules, RNA interference and antisense oligonucleotides. AC Immune expects to present six-month PET results on its ACI.24.060 vaccine in the first half and 12-month data in the second. Vaccinex could produce a Phase 3 readout for its semaphorin antibody pepinemab in the second half. Prothena and Bristol Myers Squibb should release Phase 2 results of its anti-tau antibody PRX-005 in the second half. Athira may offer top-line Phase 2/3 data on fosgonimeton in

the second half, and Anavex Life Sciences could publish full results of the Attention-AD trial of blarcamesine.

By year-end, Cassava Sciences should present Phase 3 data from the Rethink-Alz trial of simufilam, while Alector and AbbVie release Phase 2 Invoke trial results of AL002, with a go/no go decision expected subsequently (Figure 15).

Figure 15: Select Clinical Data in 2024

Company	Drug	Catalyst	Date
AC Immune	ACI.24.060	Initial 6-month PET amyloid reduction data	1H24
Alector/AbbVie	AL002	Phase 2 Invoke trial results in early Alzheimer's	4Q24
Alnylam/Regeneron	ALN-APP	Initial Phase 1b multi-dose results in early onset Alzheimer's	late 2024
Alzheon	Valiltramiprosate	Topline Phase 3 Apollo-E4 results	3Q24
Anavex	Blarcamesine	Publish full Phase 2b/3 results of AD-004 trial	1H24
Annovis Bio	Buntanetap	Topline Phase 2/3 data in mild-to-moderate Alzheimer's	April-2024
Athira	Fosgonimeton	Topline Lift-AD Phase 2/3 results	2H24
Cassava Sciences	Simufilam	Phase 3 Rethink-Alz data in mild-to-moderate Alzheimer's	late 2024
Cognition Therapeutics	CT1812	Topline Phase 2 Shine data in mild-to-moderate Alzheimer's	mid-2024
Eli Lilly	Donanemab	Primary 6-month results of Trailblazer-Alz 6 (dosing/ARIA study)	2Q24
Lexeo Therapeutics	LX1001	Interim Phase 1/2 results (all cohorts)	2H24
NewAmsterdam Pharma	Obicetrapib	Phase 2a results in early Alzheimer's (ApoE4 carriers)	2024
Prothena/Bristol-Myers Squibb	PRX005 (BMS-986446)	Early data from multiple ascending dose cohort	2024
Sage Therapeutics	Dalzanemdor	Topline Phase 2 Lightwave trial data in early Alzheimer's	2H24
UCB Group/Roche	Bepranemab	Phase 2 results in early Alzheimer's	2H24
Vaccinex	Pepinemab	Results from the Signal-AD Phase 3 trial	2H24

Source: Company Filings, Bloomberg Intelligence

Bloomberg Intelligence BI

Section 8. Prescriber Survey

Doctors Signal Slow Adoption of Anti-Amyloid Antibodies

Prescribers in our survey expected significant challenges to diagnosing and putting patients on Leqembi so if Lilly's donanemab is approved, it could exceed sales of the Biogen and Eisai drug within 12 months. The October survey of 75 physicians found that 22% said they wouldn't prescribe anti-amyloid antibodies in the following 12 months, dropping to 14% at 24 months.

8.1 Donanemab Is Expected to Quickly Overtake Leqembi

In the 12 months following the survey US prescribers expected 40% of Alzheimer patients to be on Leqembi and 29% on donanemab (Figure 16). At 24 months, though, Leqembi use dropped to 30% and donanemab's increased to 36%. In the EU and the UK, prescribers show no significant preference for either drug, with slow uptake for both.

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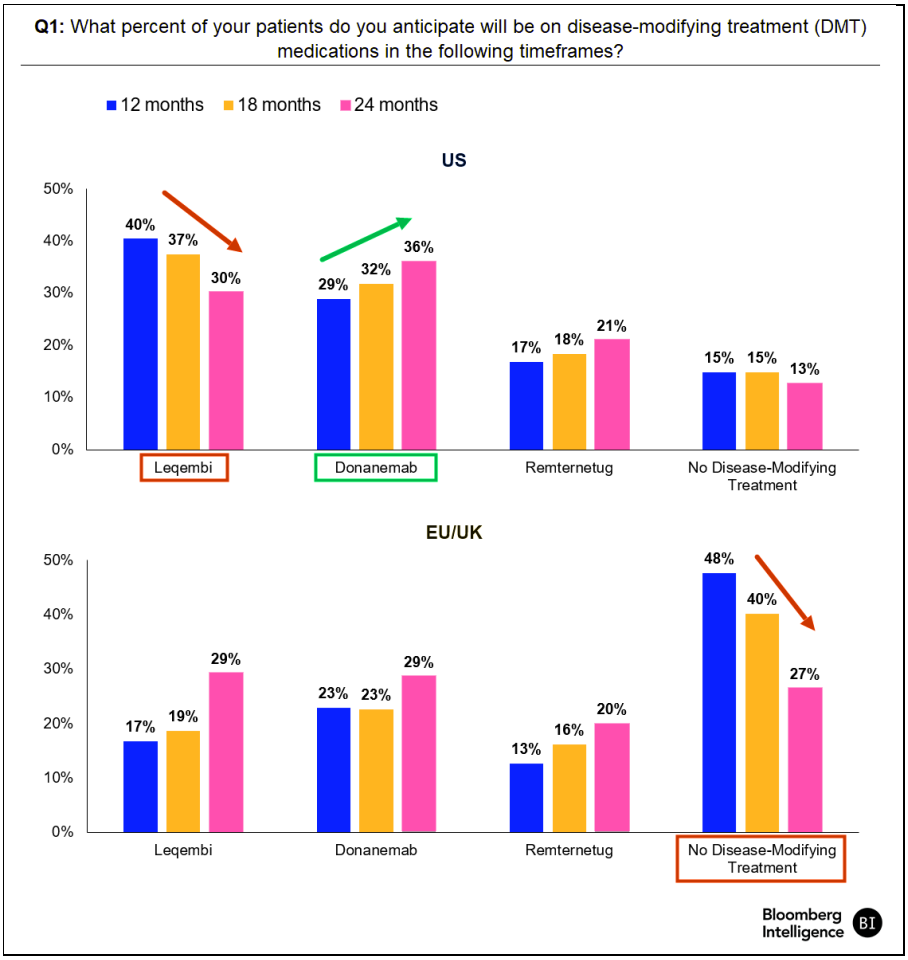
Donanemab is expected to take prescriptions from Leqembi in the US but not in Europe.

Figure 16: Physician Views on Disease-Modifying Treatments

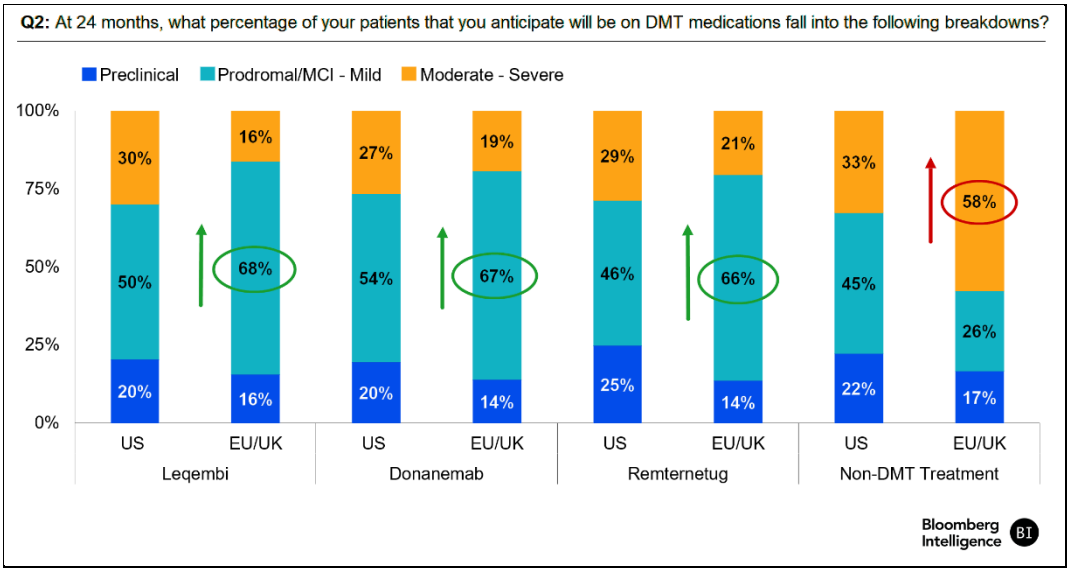


Source: Bloomberg Intelligence

Approved and late-stage anti-amyloid antibodies have focused on treating patients with prodromal cognitive impairment or mild dementia due to Alzheimer's, representing about 50% of addressable patients in the US, the EU and the UK, according to our survey. When asked what the breakdown of their patients on anti-amyloid antibodies would look like in 24 months, respondents in the EU and the UK said 67% would fall into the populations studied in these trials (prodromal and mild dementia) compared with only 50% in the US.

Continued clinical trials aim to fill knowledge gaps but given the lack of safety and efficacy data in preclinical and moderate to severe dementia patients, off-label use could be just an incremental factor.

Figure 17: Physician Views on Patient Use of Disease-Modifying Treatments at 24 months

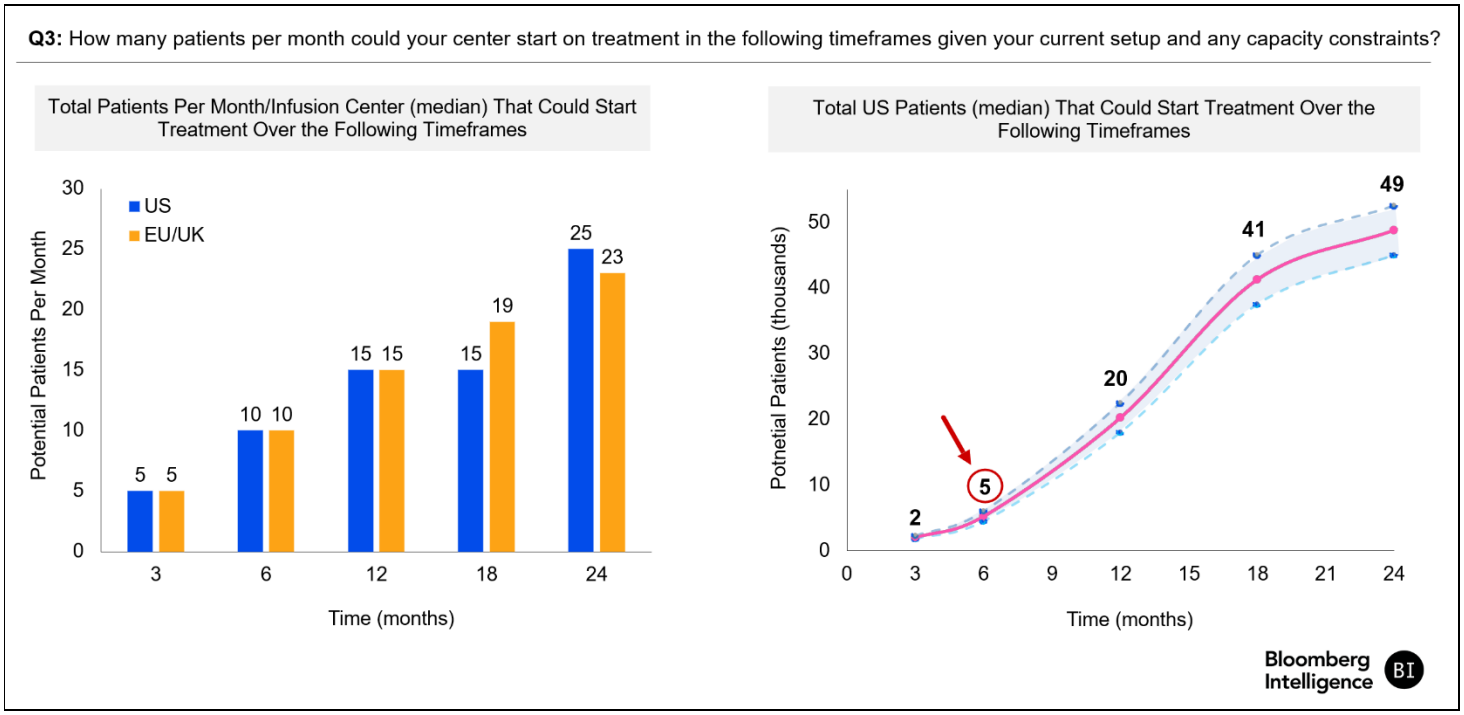


Source: Bloomberg Intelligence

When Leqembi's full approval was at hand, Biogen and Eisai said they aimed to treat 10,000 patients by the end of the first quarter, but that was too optimistic. Prescribers in our survey estimated that a median of five patients a month could start infusions over the following three months, doubling at six and plateauing at 15 patients monthly in the next 12-18 months. That would put treated patients in the US at 8,500-11,500 by the end of the third quarter, assuming 20-30% penetration of total infusion centers.

If similar exclusion criteria from clinical trials are used in practice, only about 5% of patients would qualify for treatment, according to a Mayo Clinic study, further limiting patient growth.

Figure 18: Treated Patient Estimates Highlight Slow Uptake



Source: Bloomberg Intelligence

Of Alzheimer's patients, 66-67% will be on anti-amyloid antibodies by 2030, our survey suggested. That's to be expected given the approval of Leqembi and the potential clearance this year of other anti-amyloid agents, including donanemab, its subcutaneous formulation remternetug and the subcutaneous version of Leqembi. Prescribers in the US, the EU and the UK reported a slight preference for donanemab over Leqembi but in general, they expected 20% of patients will be on Leqembi, 20% on remternetug and 25% on donanemab by 2030.

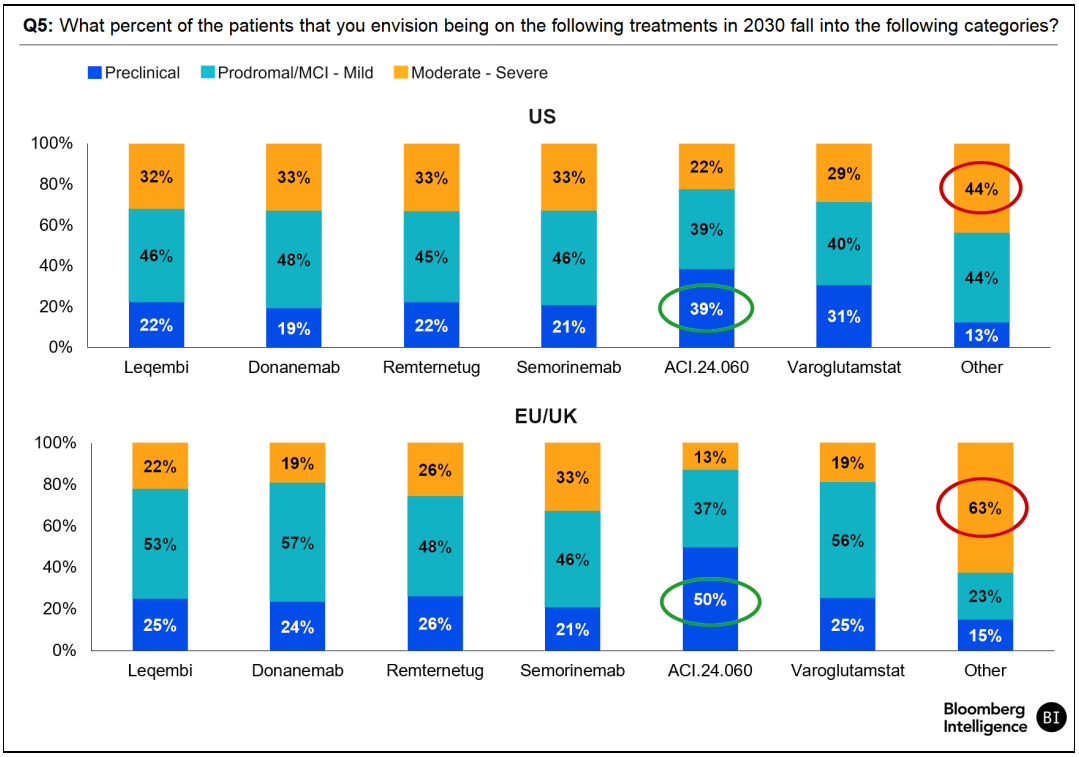
Anti-tau agents like semorinemab, oral amyloid-reducing agents such as varoglutamstat and amyloid vaccines like ACI.24.060 would be used in only about 10% of patients each, likely due to the addressable populations studied: people with preclinical and moderate to severe Alzheimer's.

8.2 Doctors See Vaccines Gaining Traction for Early Treatment

Disease-modifying therapy mostly would be used for patients who have prodromal or mild dementia from Alzheimer's, our survey showed, while 33% of anti-amyloid antibody prescriptions would be for moderate to severe dementia in the US and 20% in the EU and the UK.

For patients with preclinical Alzheimer's – about 15 million in the US alone – 48% of prescribers anticipated using anti-amyloid vaccines like AC Immune's ACI.24.060, in contrast to only 15% for people with moderate to severe dementia. Patients with advanced Alzheimer's are expected to continue symptomatic treatment, as reported by 63% of prescribers in the EU and the UK and 44% of those in the US.

Figure 19: Physician Views on Use of Disease-Modifying Treatments by 2030



Source: Bloomberg Intelligence

Timely diagnosis and treatment of Alzheimer's is hobbled by a lack of accessible biomarkers that can reliably detect disease presence, predict progression or determine whether novel disease-modifying treatments are working as intended. Fluid biomarkers provide indications of disease stage but aren't strong predictors of progression or treatment response and most are measured using invasive cerebrospinal fluid tests.

Blood-based biomarkers may enable earlier diagnoses and aid in risk assessment, early detection and prognosis. When asked which such markers have the potential for clinical use, prescribers clearly indicated high confidence in phosphorylated tau, with little confidence in total tau, GFAP, AB42 and neurofilament light chain.

Infusion-center locations and launch readiness are key factors that will dictate the initial dynamics for this novel class of disease-modifying Alzheimer's drugs. Leqembi and donanemab will require onerous patient screening – to identify who will truly benefit and inform those at greater risk – as well as complex infusion, safety monitoring and care dynamics. Of the prescribers surveyed, 71% are in urban centers and 29% are in the suburbs, in line with infusion-center distribution in the US, as reported by the National Infusion Center Association.

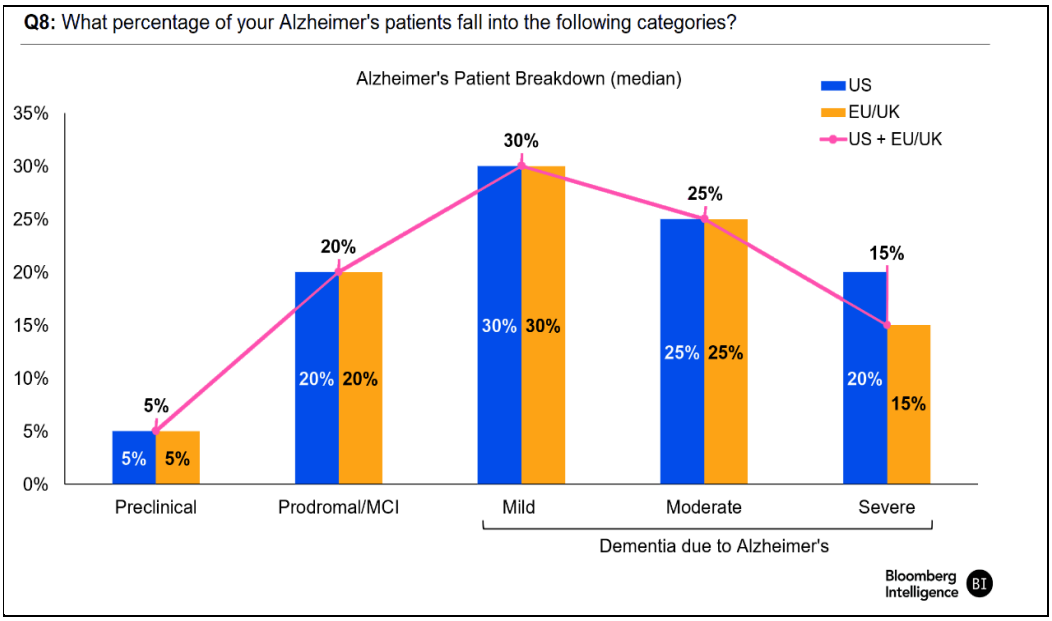
Most prescribers agreed that there are enough specialists in their area to meet the anticipated increase in demand for new Alzheimer's medications in urban centers and suburbs, though so far that hasn't always been the case.

8.3 Screening, Side Effects Pose Risk to Anti-Amyloid Use

Trials for most disease-modifying treatments focused on patients with mild (prodromal) cognitive impairment or mild dementia due to Alzheimer's. To better assess the market potential of the therapies, we aimed to define the real-world distribution of patients. Half fell into the categories included in the clinical studies, with 20% affected by prodromal cognitive impairment and 30% by mild.

These distributions were similar in urban centers and suburbs, as well as in the US, the EU and the UK.

Figure 20: Stratification of Alzheimer's Patients Seeking Care



Source: Bloomberg Intelligence

Patient access and reimbursement for disease-modifying drugs are key concerns. Medicare has agreed to cover novel anti-amyloid antibodies for patients that enroll in a registry designed to collect real-world safety and efficacy data from those with prodromal or mild dementia with evidence of amyloid pathology. Yet various screening and safety monitoring protocols could present logistical hurdles to widespread use.

Of the 75 prescribers surveyed, 81% anticipate issues with cost and insurer coverage, 59% are concerned about safety and 55% believe amyloid screening will represent the biggest challenge. Patient adherence and infusion-center capacity were also substantial concerns, noted by close to 50% of respondents.

Biogen and Eisai's Leqembi and Lilly's donanemab have different infusion frequencies, treatment duration and cessation protocols once amyloid-lowering thresholds (about 24 centiloids) are achieved. Prescribers have mixed views about the treatment duration. Of those surveyed, 53% in the US and 24% in the EU and the UK plan to treat patients for 46 weeks, regardless of therapy

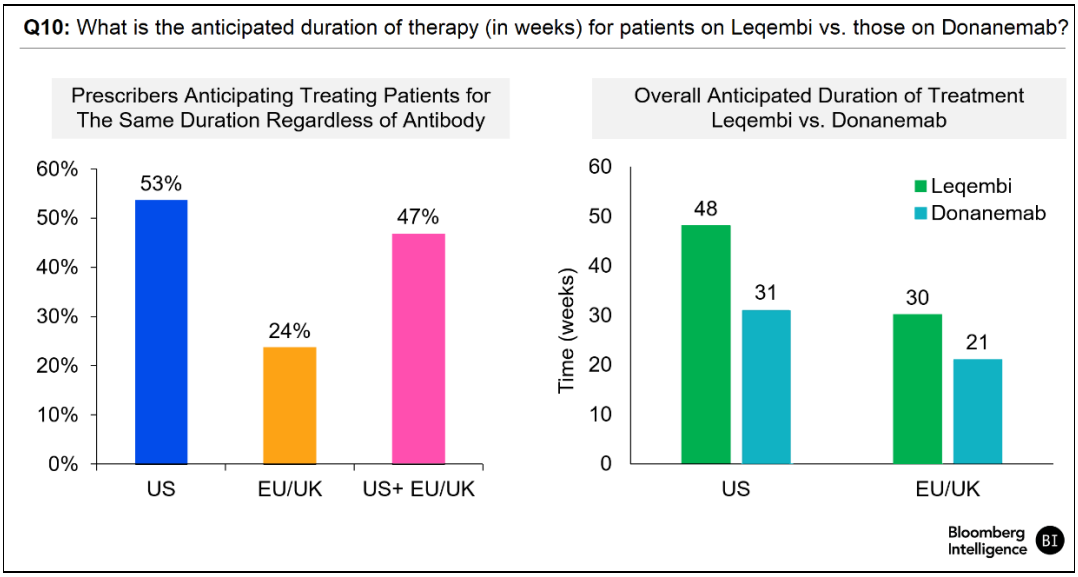
used. Physicians in the US aim to infuse Leqembi for 48 weeks and donanemab for 31, while those in the EU and the UK plan to infuse Leqembi for 30 weeks and donanemab for 21.

The median projected durations across regions surveyed are 33 weeks for donanemab and 47 for Leqembi.

BI

Donanemab's trial was designed to stop infusions after reaching amyloid negativity, while Leqembi is administered continuously, even after reaching clearance.

Figure 21: Duration of Treatment With Anti-Amyloid Antibodies



Source: Bloomberg Intelligence

When it granted full approval of Leqembi in July, the FDA made significant changes to the drug label that had been issued on conditional approval, strengthening language in a boxed warning on the risk of amyloid-related imaging abnormalities, which requires extensive training to detect and manage. Of the prescribers surveyed, 25% felt very confident of detecting ARIA, 60% felt somewhat confident and 15% reported little confidence and would prefer to consult a specialist. ARIA will likely be more common in real-world patients than in trials since comorbidities in this aging population can lead to exclusion from clinical trials.

Since Alzheimer's is heterogeneous, determining which patients will truly benefit and which are most at risk is critical. The relationship between ApoE4 status and ARIA is becoming clear, with the Leqembi boxed warning highlighting the importance of genetic testing before starting treatment. Donanemab data showed that those with higher p-tau217 levels benefited less from treatment, indicating the importance of tau quantification as a patient-selection tool.

Of prescribers in the EU and the UK, 76% plan to use genetic testing and tau quantification for patient selection, compared with just 50% in the US. Inadequate screening could lead to greater ARIA rates in the real world than in trials – potentially derailing the launch of these novel treatments.

Section 9. Medicare Outlook

Drug Coverage Limits Likely Remain for the Near Term

Medicare will cover FDA-approved Alzheimer's drugs for enrollees diagnosed with mild cognitive impairment or mild Alzheimer's dementia and participating in a registry with follow-up care. That decision is likely to remain frozen for the near term as the agency collects more real-world data on health effects. Members of Congress have voiced concerns with the limits, but lawmakers are unlikely to pass near-term legislation that might speed reconsideration of the decision.

There aren't many near-term catalysts that would require the Centers for Medicare and Medicaid Services to update its coverage for the use of amyloid antibodies. FDA approval of Lilly's donanemab is possible this year, but reconsideration of national coverage takes 9-12 months. Medicare's decision to remove restrictions on amyloid PET scans could improve access to the drugs.

9.1 Bill Would Speed Reconsideration of Medicare Decisions

Though the CMS has faced months of congressional and stakeholder pressure for a revision of its Alzheimer's coverage decision, the agency has maintained that additional real-world evidence collection through a registry is needed to better understand the impact on outcomes in a broad community setting. The data could then be used to update coverage if warranted.

A bill has been introduced that would require the Medicare agency to reconsider a coverage decision on request and complete the review more quickly than the current 9-12 months. The legislation would also allow newly approved FDA drugs to be considered individually if there's a restrictive national coverage determination in place for the class. But there isn't congressional appetite to legislate Medicare's coverage process, and this year's election leaves little opportunity for further debate, which will likely be revisited when more safety and effectiveness data is available.

Medicare's removal of national restrictions on amyloid PET scans should help with adoption of new Alzheimer's therapies, but it might be the last incremental update to coverage policy in the area. Medicare will allow regional officials or Medicare administrative contractors to make coverage decisions. Though policy only affects coverage in the respective regions, the CMS believes that its decision will lead to consistent coverage. The new policy could allow physicians to screen patients multiple times to diagnose and assess how a drug is working or to stop treatment because of side effects.

Section 10. Performance and Valuation

Market Potential Is Likely to Materialize Gradually

Biotech and large cap pharmaceuticals have underperformed the broader market over the past year, with the SPDR S&P Biotech ETF rising about 6%, compared with 24% for the S&P 500. Though a slower-than-expected launch for Biogen and Eisai's Leqembi didn't help pharmaceuticals, Alzheimer's treatment would be just a small portion of most large cap drugmakers' results. Antitrust scrutiny and reduced sales expectations for Covid-19 vaccines played larger roles in the sector's performance.

Biotech has started recovering lately as mergers and acquisitions began to pick up. The Nasdaq Biotech Index has climbed 23% from its 2023 low in October but has still trailed the S&P 500's 28% increase.

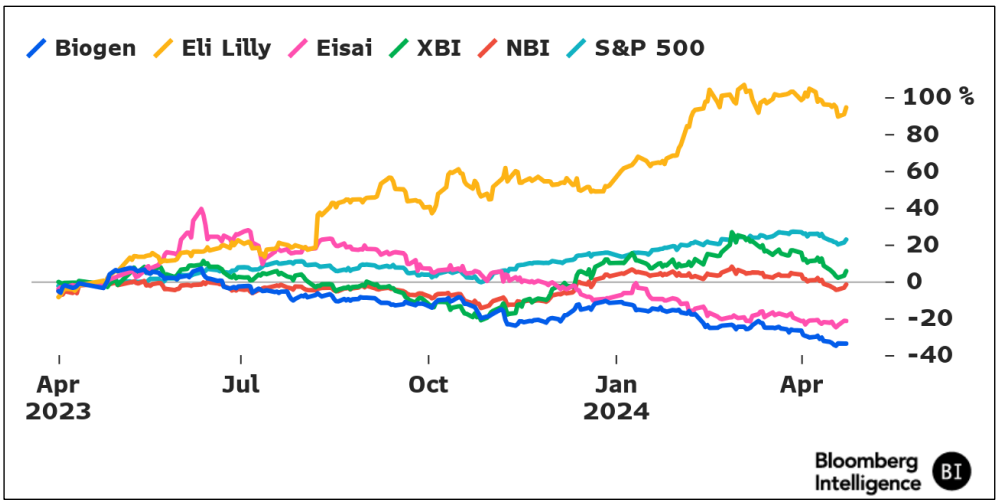
10.1 Performance: Biogen Struggles With Slow Leqembi Launch

Biogen has dropped about 51% from its high in 2021, when it gained accelerated approval for amyloid antibody Aduhelm, which ultimately failed. Increased first-quarter sales of Leqembi and Skyclarys, for the degenerative nervous system disease Friedreich ataxia, bode well but are likely insufficient to offset a declining multiple sclerosis franchise.

Biogen has tumbled 19% and Eisai 31% since Leqembi was granted full approval in July. Continued gains in Leqembi prescriptions is key for Biogen's growth prospects, with consensus expecting a 10% contribution to the bottom line in 2027 and almost double that by 2030. Lilly has been unscathed by regulatory delays for donanemab. The stock's 87% advance over the past year has been driven by growth in its tirzepatide diabetes and weight-loss franchise, which is expected to account for 35% of total revenue this year.

Small-cap drugmakers that have yet to generate sales are prone to volatile performance on company news. Vivoryon Therapeutics' latest clinical update is an example, prompting the shares to lose almost all their value after its Phase 3 study failed to show a benefit. Even later-than-expected clinical readouts can have a large impact, with Prothena's delay for its Alzheimer's drug driving a 46% decline.

Figure 22: Stock Performance for Commercial Biotechs Active in Alzheimer's



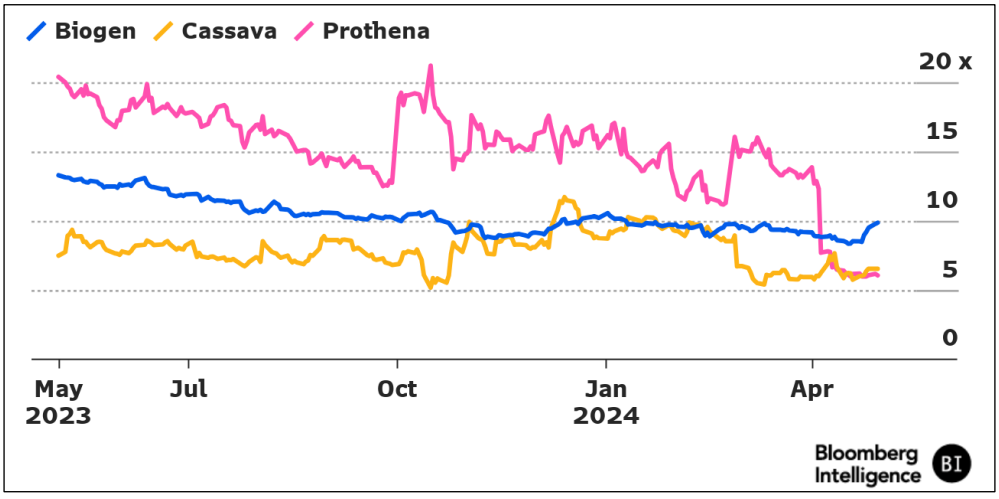
Source: Bloomberg Intelligence

10.2 Valuation: Low Multiples Reflect Elevated Risk

Biogen trades at 9.8x blended forward 12-month earnings, compared with an average of 12.7x for large biotech peers, reflecting delays and other challenges to Leqembi's rollout. The multiple has dropped from 12.9x when the drug gained full approval in July. Success in Alzheimer's is key for Biogen to sustain long-term growth as its core products continue to decline.

Cassava and Prothena, as early-stage biotechs focusing on Alzheimer's with no approved products, have modest valuations: 6.5x for Cassava and 6.1x for Prothena. Those likely stem from skepticism in their mechanisms and the difficulty of obtaining approval for Alzheimer's. Prothena's drop from a peak of 21.2x probably was fueled by delays in its Alzheimer's trial readouts.

Figure 23: Best Price/2028 Earnings Ratio for Biotechs Active in Alzheimer's



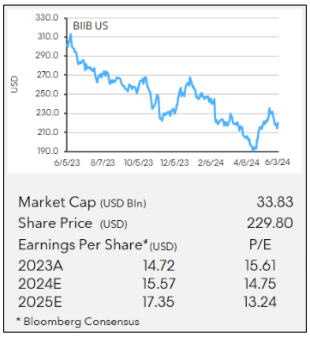
Source: Bloomberg Intelligence

Section 11. Company Impacts

Overcoming Approval Hurdles, Launch Challenges

Biogen and Eisai are increasing efforts to increase Leqembi prescriptions after its disappointing launch, especially since Lilly could gain approval for its competing anti-amyloid antibody by year-end. Novo Nordisk hopes to get results next year confirming that its semaglutide could benefit some Alzheimer's patients.

11.1 Biogen Needs Momentum From Leqembi, Skyclarys



Market Cap (USD Bln)		33.83
Share Price (USD)		229.80
Earnings Per Share* (USD)		P/E
2023A	14.72	15.61
2024E	15.57	14.75
2025E	17.35	13.24

* Bloomberg Consensus

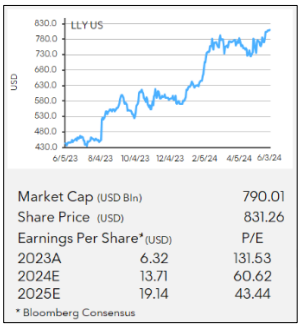
$3 Billion
Consensus for 2030 Leqembi US revenue

0.3%
Estimated CAGR for 2022-27

Company Outlook: Biogen's core products are in decline and its best shot at near-term growth comes from recently acquired Skyclarys for Friedreich ataxia, which is expected to drive operating and top-line revenue in 2024. Leqembi could deliver $3 billion in peak US sales for Alzheimer's, but logistical hurdles are likely to persist, delaying any meaningful revenue until at least 2025. Continued cost cuts that are designed to realize about $800 million in net operating expense savings by 2025 make sense, especially given Biogen's high-risk pipeline. The company's biosimilar business isn't core, making a divestiture likely.

Alzheimer's Impact: Biogen aims to treat earlier stages of Alzheimer's, with a goal of unlocking a much larger market of asymptomatic patients. The company is looking beyond anti-amyloid therapy, joining with Ionis on BIIB-080, an antisense oligonucleotide that has shown promising early results. Though consensus sees Alzheimer's drugs accounting for only 0.9% of total revenue this year, that increases to 19% by 2030, which will be difficult to achieve after a slow launch. Estimates have deteriorated, now projecting a 3% sales decline this year instead of a 2% drop previously and the projected 2022-27 compound adjust growth rate falling to 0.3% from 3%.

11.2 Lilly Obesity Franchise Makes Up for Alzheimer's Delays



Market Cap (USD Bln)		790.01
Share Price (USD)		831.26
Earnings Per Share* (USD)		P/E
2023A	6.32	131.53
2024E	13.71	60.62
2025E	19.14	43.44

* Bloomberg Consensus

$4.5 Billion

US donanemab revenue estimated for 2030

$1.9 Billion

US remternetug revenue expected for 2030

Company Outlook: Lilly's growth outlook exceeds that of most peers and drives a premium valuation in its sector, but long-term consensus may need to go higher still. Zepbound and Mounjaro for obesity and diabetes could top expectations, though the sales potential of both means the market may be ruthless about any minor setbacks. Risk centers on consensus for operating margin progression, given the likely marketing support needed for launches, investment for cost of goods sold and continued R&D scale-up. Donanemab is a wild card.

Alzheimer's Impact: We expect donanemab to gain approval by year-end, given its efficacy and safety profile. Lilly has remained largely unaffected by regulatory delays on the Alzheimer's drug, thanks to success with its tirzepatide franchise for diabetes and weight loss. Lilly's subcutaneous anti-amyloid remternetug could enter the market by 2026. The company also is developing tau-lowering agents, which could allow it to increase market share in more advanced patient populations. Alzheimer's is estimated to account for 0.1% of total revenue this year if donanemab is approved, increasing to 5% by 2030.

11.3 Novo Nordisk Aims to Expand Semaglutide to Alzheimer's

Market Cap (DKK Bln)		4,180.13
Share Price (DKK)		923.90
Earnings Per Share* (DKK)		P/E
2023A	18.62	49.62
2024E	23.58	39.18
2025E	28.78	32.11

* Bloomberg Consensus

2H25

Primary Evoke and Evoke+ semaglutide data due for Alzheimer's

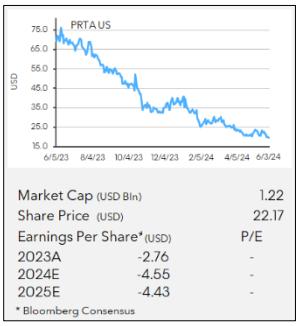
$44.9 Billion

Oral semaglutide revenue estimated for 2030

Company Outlook: Novo Nordisk's growth prospects give it a premium valuation compared with peers, with gains bolstered by its GLP-1 drugs for diabetes and obesity though supply remains a near-term limiting factor. The company's Ozempic and Wegovy compete against Lilly's Mounjaro and Zepbound, which are more effective. Yet with relatively low GLP-1 penetration rates, there's ample space for both companies. Robust outcomes data support broad reimbursement for Wegovy. An oral offering could unlock the obesity market further, though launch is unlikely before 2026. The solid pipeline includes a potential response to Mounjaro and Zepbound.

Alzheimer's Impact: Novo hopes to expand its semaglutide franchise beyond obesity, diabetes and comorbid cardiovascular disease. Two large Phase 3 studies, Evoke and Evoke+, are underway in early Alzheimer's, with primary results of the 104-week trial slated for the second half of 2025. The pivotal trials were based on retrospective analysis, which presents risk. If successful, Alzheimer's could be the first approved neurology indication for semaglutide. Cerebralspinal fluid biomarker analysis should help identify patients that could benefit from the approach. Given the success of Novo's obesity and diabetes franchise, a label expansion for Alzheimer's would bring additional upside with minimal development risk.

11.4 Prothena May Get Its First Sales From Amyloidosis Drug



Market Cap (USD Bln)		1.22
Share Price (USD)		22.17
Earnings Per Share* (USD)		P/E
2023A	-2.76	-
2024E	-4.55	-
2025E	-4.43	-

* Bloomberg Consensus

$1.2 Billion

Consensus for 2030 revenue

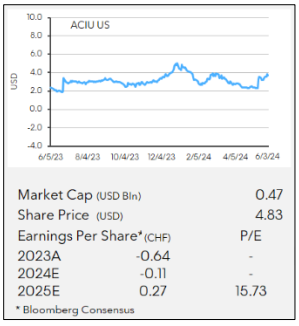
2028

Estimated first year to generate profit

Company Outlook: Prothena's first shot at near-term revenue will likely come from its lead program, a Phase 3 trial of birtamimab for amyloid light-chain amyloidosis, which may reach market next year. With a diversified pipeline focused on protein dysregulation, the company is poised to leverage various clinical-stage assets that could unlock neurology indications including Parkinson's, Alzheimer's and amyotrophic lateral sclerosis. Partnerships with Roche, Novo and Bristol Myers should speed development of its late-stage pipeline.

Alzheimer's Impact: Prothena's first revenue likely will come from its amyloidosis asset, with approval of its anti-tau antibody PRX005 in Alzheimer's possible by 2026. Its second Alzheimer's construct in the clinic is PRX012, a self-injectable anti-amyloid antibody that could compete with Biogen and Eisai's lecanemab and Lilly's remternetug but isn't likely to launch before 2027. Its third, PRX123, a dual target amyloid beta-tau vaccine, is slated to begin clinical testing this year. Meaningful contributions from its Alzheimer's franchise aren't likely before 2030 since its pipeline is in the early to middle stages.

11.5 AC Immune's Amyloid Vaccine Gains Momentum



Market Cap (USD Bln)		0.47
Share Price (USD)		4.83
Earnings Per Share* (CHF)		P/E
2023A	-0.64	-
2024E	-0.11	-
2025E	0.27	15.73

* Bloomberg Consensus

$2.1 Billion

Potential milestone payments from Takeda

2028

First product launch

Company Outlook: By combining diagnostics and therapeutics development, AC Immune can contribute to detecting and treating Alzheimer's. Its recent partnership with Takeda Pharmaceutical will support development of its lead amyloid beta vaccine candidate, ACI.24.060, with AC Immune receiving $100 million upfront, as much as $2.1 billion in potential milestone payments and royalties. AC Immune also has a p-tau vaccine in development in partnership with Janssen Biotech and wholly owned tau and amyloid antibodies. Its extensive pipeline could shift treatment toward precision medicine and disease prevention.

Alzheimer's Impact: The biotech's platform is set to deliver novel therapeutics and diagnostics for Alzheimer's and other neurodegenerative diseases. Its first therapeutic product isn't expected to launch until 2028, though a tau imaging diagnostic could reach patients by 2026. As its pipeline begins to click, derisking its platform technology remains a key step to accelerating its programs. Disease-modifying vaccine pricing remains a wildcard but could make meaningful contributions within three years of launch, given the large unmet need.

Section 12. Glossary

Allele: An alternative form of gene contained in chromosomes that influence how cells work; The two alleles in a gene pair are inherited, one from each parent

Amyloid: A peptide produced through cleavage of a transmembrane protein, amyloid precursor protein, by β- and γ-secretases; Amyloid-beta (Aβ) peptide is believed to be a main cause of Alzheimer's disease

Amyloid hypothesis: Proposes amyloid-β as main cause of Alzheimer's and suggests that the misfolding of amyloid-β leads to its accumulation in senile plaques and the deposition of misfolded tau protein, resulting in personality and cognitive decline

ApoE-e4: An allele associated with increased risk of developing Alzheimer's dementia; About 25% of people carry one copy and 3% carry two

Autosomal: One of the 22 pairs of numbered chromosomes, as opposed to the sex chromosomes XX and XY

Dementia: Final stage in Alzheimer's continuum, when a person has severe episodic memory loss and functional impairment leading to a loss of independence; Dementia can be categorized as mild, moderate or severe

Disease-modifying therapy: A treatment that slows or reverses progression of a disease by targeting its underlying cause; Contrasts with treatment of symptoms only

Early Alzheimer's: Encompasses the prodromal or mild cognitive impairment phase and mild dementia due to Alzheimer's

Peptide: A short chain of amino acids that make up longer chain polypeptides; Proteins are formed by various polypeptides that can be cleaved into short peptide fragments

Preclinical or asymptomatic Alzheimer's: First stage in continuum from normal aging toward Alzheimer's dementia; Remains difficult to diagnose and predict progression in individual patient and mainly is used in research

Prodromal or mild cognitive impairment: Experience of episodic memory loss that may lead to dementia

Proteinopathies: Group of diseases caused by misfolded proteins, leading to aggregates

Synapse: Space between two nerve cells (neurons) that allows electrical and chemical signals to be transmitted

Synaptic plasticity: Ability of synapses to strengthen or weaken over time in response to increases or decreases in their activity

Tau: A microtubule-associated protein that forms insoluble filaments that can accumulate as neurofibrillary tangles in Alzheimer's and related tauopathies

Section 13. Full Pipelines

Figure 24: Amyloid Lowering Pipeline

Company	Drug	Drug Profile	Phase	Trial name	Age group studied	General Mechanism	Enrollment	Patient Population	Modality	Mode of Admin.	NCT Number
Amyloid Reduction											
Biogen/Eisai/BioArctic	Lecanemab	Lecanemab	Phase III	AHEAD 3-45	55-80	Amyloid Reduction	1400	Preclinical, Early	Amyloid Monoclonal Antibody	IV	NCT04468659
Biogen/Eisai/BioArctic	Lecanemab	Lecanemab	Phase III	CLARITY-AD	50-90	Amyloid Reduction	1906	Early-to-Mild	Amyloid Monoclonal Antibody	IV, SC	NCT03887455
Alzheon	Valiltramiprosate	Valiltramiprosate	Phase III	APOLLOE4	50-80	Amyloid Reduction	300	Early-to-Mild, APOE4 Homozygotes	Tramiprosate Prodrug (Aβ Monomer Stabilizer)	Oral	NCT04770220
Eli Lilly	Donanemab	Donanemab	Phase III	TRAILBLAZER-ALZ 2	60-85	Amyloid Reduction	1800	Early-to-Mild	Amyloid Monoclonal Antibody	IV	NCT04437511
Eli Lilly	Donanemab	Donanemab	Phase III	TRAILBLAZER-ALZ 3	65-80	Amyloid Reduction	2600	Preclinical	Amyloid Monoclonal Antibody	IV	NCT05026866
Eli Lilly	Donanemab	Donanemab	Phase III	TRAILBLAZER-ALZ 5	60-85	Amyloid Reduction	1500	Early-to-Mild	Amyloid Monoclonal Antibody	IV	NCT05508789
Eli Lilly	Donanemab	Donanemab	Phase III	TRAILBLAZER-ALZ 6	60-85	Amyloid Reduction	800	Early-to-Mild	Amyloid Monoclonal Antibody	IV	NCT05738486
Eli Lilly	Remternetug	Remternetug	Phase III	TRAILRUNNER-ALZ 1	60-85	Amyloid Reduction	600	Early-to-Mild	Amyloid Monoclonal Antibody	IV, SC	NCT05463731
Biogen/Eisai/BioArctic	Lecanemab	Lecanemab	Phase II		50-90	Amyloid Reduction	856	Early-to-Mild	Amyloid Monoclonal Antibody	IV	NCT01767311
Alzheon	Valiltramiprosate	Valiltramiprosate	Phase II		50-80	Amyloid Reduction	84	Early-to-Mild, APOE4 Homozygotes	Tramiprosate Prodrug (Aβ Monomer Stabilizer)	Oral	NCT04693520
Eli Lilly	Donanemab	Donanemab	Phase II	TRAILBLAZER-EXT	60-90	Amyloid Reduction	90	Early-to-Mild	Amyloid Monoclonal Antibody	IV	NCT04640077
Atridia	SHR 1707	SHR 1707	Phase II		55-85	Amyloid Reduction	45	Early-to-Mild	Amyloid Monoclonal Antibody	IV	NCT06199037
Actinogen	Xanamem	Xanamem	Phase II	XanaMIA	50+	Amyloid Reduction	220	Mild-to-Moderate	Cortisol reduction	Oral	NCT06125951
AbbVie	ABBV-916	ABBV-916	Phase II	HARBOR	50-90	Amyloid Reduction	195	Early-to-Mild	Amyloid Monoclonal Antibody	IV	NCT05291234
PRInnovation GmbH	PRI 002	PRI 002	Phase II	PRImus-AD	55-80	Amyloid Reduction	270	Early-to-Mild	Anti-prionic Amyloid Oligomers	Oral	NCT06182085
Roche	Trontinemab	Trontinemab	Phase I/II	BRAINSHUTTLE-AD	50-85	Amyloid Reduction	210	Early-to-Mild	Amyloid Monoclonal Antibody	IV	NCT04639050
AC Immune	ACI-24.060	ACI-24.060	Phase I/II	ABATE	35-75	Amyloid Reduction	140	Early	Anti-amyloid liposomal vaccine	SC	NCT05462106
Lexeo Therapeutics	LX1001	LX1001	Phase I/II	APOE4	50+	Amyloid Reduction	15	Early-to-Moderate	Gene Therapy (AAV)	Intrathecal	NCT03634007
Alzamend Neuro	ALZN 002	ALZN 002	Phase I/II		60-85	Amyloid Reduction	30	Mild-to-Moderate	Anti-amyloid vaccine (antigen-activated)	IV	NCT05834296
ProMIS Neurosciences	PMN 310	PMN 310	Phase I		18-65	Amyloid Reduction	40	Healthy volunteers	Amyloid modulator	IV	NCT06105528
Alnylam/Regeneron	ALN-APP	ALN-APP	Phase I		18+	Amyloid Reduction	60	Early	APP silencing (C16-siRNA)	Intrathecal	NCT05231785
Prothena	PRX012	PRX012	Phase I	ASCENT-1		Amyloid Reduction		Early-to-Mild	Amyloid Monoclonal Antibody	SC	
Prothena	PRX012	PRX012	Phase I	ASCENT-2		Amyloid Reduction		Early-to-Mild	Amyloid Monoclonal Antibody	SC	
Lexeo Therapeutics	LX1001	LX1001	Phase I	LEADLTFU	50+	Amyloid Reduction	15	Early-to-Moderate, APOE4 Homozygotes	Gene Therapy (AAV)	Intrathecal	NCT05400330
Eli Lilly	Remternetug	Remternetug	Phase I		18-85	Amyloid Reduction	224	Early-to-Mild	Amyloid Monoclonal Antibody	SC, IV	NCT04451408
Alzinova	ALZ-101	ALZ-101	Phase I		50-80	Amyloid Reduction	33	Early	Anti-Amyloid Vaccine	IM	NCT05328115
Nuravax	AV-1959D	AV-1959D	Phase I		60-85	Amyloid Reduction	48	Early	Anti-Amyloid DNA-based Vaccine	ID	NCT05642429
Atridia	SHR 1707	SHR 1707	Phase I		55-85	Amyloid Reduction	16	Early-to-Mild	Amyloid Monoclonal Antibody	IV	NCT06114745
Atridia	SHR 1707	SHR 1707	Phase I		55-85	Amyloid Reduction	41	Early-to-Mild	Amyloid Monoclonal Antibody	IV	NCT05681819

Source: Bloomberg Intelligence

Figure 25: Tau Lowering Pipeline

Company	Drug	Drug Profile	Phase	Trial name	Age group studied	General Mechanism	Enrollment	Patient Population	Modality	Mode of Admin.	NCT Number
Tau Reduction											
Biogen/Ionis	BIIB080	BIIB080	Phase II	CELIA	50-80	Tau Reduction	735	Early-to-Mild	Tau antisense oligonucleotide	Intrathecal	NCT05399888
Johnson & Johnson	JNJ 63733657	JNJ 63733657	Phase II	AUTONOMY	55-80	Tau Reduction	523	Early	P-Tau monoclonal antibody	IV	NCT04619420
Eli Lilly	LY3372689	LY3372689	Phase II		60-85	Tau Reduction		Early	O-GlcNAcase Inhibitor	Oral	NCT05063539
Annovis Bio	Buntanetap	Buntanetap	Phase II		55-85	Tau Reduction	320	Mild	Tau aggregation inhibitor	Oral	NCT05686044
UCB Biopharma/Roche	Bepranemab	Bepranemab	Phase II		50-80	Tau Reduction	421	Mild	Tau monoclonal antibody	IV	NCT04867616
Eisai	E2814	E2814	Phase I/II		18-80	Tau Reduction		Mild	Tau monoclonal antibody	IV	NCT04971733
Aprinoia Therapeutics	APNmab 005	APNmab 005	Phase I		18-65	Tau Reduction	40	Healthy volunteers	Tau monoclonal antibody	IV	NCT05344989
Alzheimer's Disease Expert Lab (ADEL), Inc.	ADEL-Y01	ADEL-Y01	Phase I		18-80	Tau Reduction	73	Early	Tau monoclonal antibody	IV	NCT06247345
Prothena/BMS	PRX005	PRX005	Phase I			Tau Reduction			Tau tri-epitopic antibody	IV	
Oligomerix	OLX-07010	OLX-07010	Phase I		18-75	Tau Reduction	88		Tau aggregation inhibitor	Oral	NCT05696483
Novartis	NIO-752	NIO-752	Phase I		30-74	Tau Reduction	24	Early	Tau antisense oligonucleotide	Intrathecal	NCT05469360
Merck Sharp & Dohme	MK-2214	MK-2214	Phase I	MK-2214-02	50-80	Tau Reduction	48	Mild-to-moderate	Tau monoclonal antibody	IV	NCT05466422
Arvinas	Tau-PROTAC	Tau-PROTAC	Preclinical			Tau Reduction			Tau protein degrader	Oral	

Source: Bloomberg Intelligence

Figure 26: Amyloid and Tau Lowering Pipeline

Company	Drug	Drug Profile	Phase	Trial name	Age group studied	General Mechanism	Enrollment	Patient Population	Modality	Mode of Admin.	NCT Number
Amyloid and Tau Reduction											
AB Science	Masitinib	Masitinib	Phase III		50+	Amyloid and Tau Reduction	600	Mild-to-moderate	TK Inhibitor with standard of care	Oral	NCT05564169
KeifeRx	Nilotinib	Nilotinib	Phase III	NILEAD	55-85	Amyloid and Tau Reduction	1275	Early	TK Inhibitor	Oral	NCT05143528
Samsung Pharmaceutical	GV1001	GV1001	Phase III		55-85	Amyloid and Tau Reduction	750	Moderate-to-Severe	Peptide Vaccine	SC	NCT05303701
Biogen/Eisai/BioArctic	Lecanemab	Lecanemab	Phase II/III	DIAN-TU	18-80	Amyloid and Tau Reduction	168	Preclinical-to-early	Amyloid monoclonal antibody and Tau monoclonal antibody (E2814)	IV	NCT05269394
Biogen/Eisai/BioArctic	Lecanemab	Lecanemab	Phase II/III	DIAN-TU-001	18-80	Amyloid and Tau Reduction	490	Preclinical-to-early	Amyloid monoclonal antibody and Tau monoclonal antibody (E2814)	IV	NCT01760005
Prothena	PRX123	PRX123	Preclinical			Amyloid and Tau Reduction			Amyloid beta-Tau vaccine		

Source: Bloomberg Intelligence

Figure 27: Synaptic Plasticity Modulators Pipeline

Company	Drug	Drug Profile	Phase	Trial name	Age group studied	General Mechanism	Enrollment	Patient Population	Modality	Mode of Admin.	NCT Number
Synaptic Plasticity											
Athira Pharma	Fosgonimeton	Fosgonimeton	Phase III	LIFT-AD	55-85	Synaptic Plasticity	554	Mild-to-moderate	HGF/MET activator (positive modulator)	SC	NCT04488419
Cassava Sciences	Simufilam	Simufilam	Phase III	RETHINK-ALZ	50-87	Synaptic Plasticity	750	Mild-to-moderate	Microfilament Modulator	Oral	NCT04994483
Cassava Sciences	Simufilam	Simufilam	Phase III	REFOCUS-ALZ	50-87	Synaptic Plasticity	1083	Mild-to-moderate	Microfilament Modulator	Oral	NCT05026177
AgeneBio	Levetiracetam	Levetiracetam	Phase III		55-85	Synaptic Plasticity	1040	Early	SV2A protein ligand	Oral	NCT05986721
Luye Pharma	Rivastigmine (transdermal)	Rivastigmine (transdermal)	Phase III			Synaptic Plasticity			Cholinesterase Inhibitor	Patch	
AriBio	AR1001	AR1001	Phase III	POLARIS-AD	55-80	Synaptic Plasticity	1150	Early-to-mild	PDE5 Inhibitor	Oral	NCT05531526
Cassava Sciences	Simufilam	Simufilam	Phase III	OLE	50-87	Synaptic Plasticity	1600	Mild-to-moderate	Microfilament Modulator	Oral	NCT05575076
Cassava Sciences	Simufilam	Simufilam	Phase III	RETHINK-ALZ	50-87	Synaptic Plasticity	750	Mild-to-moderate	Microfilament Modulator	Oral	NCT04994483
Cassava Sciences	Simufilam	Simufilam	Phase III	REFOCUS-ALZ	50-87	Synaptic Plasticity	1083	Mild-to-moderate	Microfilament Modulator	Oral	NCT05026177
Athira Pharma	Fosgonimeton	Fosgonimeton	Phase II/III		55-85	Synaptic Plasticity	450	Mild-to-moderate	HGF/MET activator (positive modulator)	SC	NCT04886063
Anavex	Blarcamesine	Blarcamesine	Phase II/III	ATTENTION-AD (OLE)	55-85	Synaptic Plasticity	450	Early	OPRS1 agonist	Oral	NCT04314934
Neurim Pharmaceuticals	Piromelatine	Piromelatine	Phase II/III		60-85	Synaptic Plasticity	225	Mild	Serotinin 2B receptor antagonist	Oral	NCT05267535
Sage Therapeutics	Dalzanemdor	Dalzanemdor	Phase II		50-80	Synaptic Plasticity	150	Mild	NMDA activator (positive modulator)	Oral	NCT05619692
Jupiter Neurosciences	Jotrol	Jotrol	Phase II			Synaptic Plasticity			SIRT1 activator	Oral	
Cassava Sciences	Simufilam	Simufilam	Phase II	Open-Label Extension	50+	Synaptic Plasticity	90	Mild-to-moderate	Microfilament Modulator	Oral	NCT05352763
CuraSen	CST-107/CST-103	CST-107/CST-103	Phase II	CLIN-011	50-85	Synaptic Plasticity		Mild	ß2-AR agonist	Oral	NCT04739423
CuraSen	CST-107/CST-103	CST-107/CST-103	Phase II		50-85	Synaptic Plasticity	60	Mild	ß2-AR agonist	Oral	NCT05104463
AbbVie (Syndesi acquisition)	ABBV 552	ABBV 552	Phase II		50-90	Synaptic Plasticity	240	Mild	SV2A Modulator	Oral	NCT05771428
CuraSen	CST 2032 (Clenbuterol)	CST 2032 (Clenbuterol)	Phase II		50-85	Synaptic Plasticity	60	Mild	ß2-AR agonist	Oral	NCT05104463
CuraSen	CST-107/CST-103	CST-107/CST-103	Phase II		50-85	Synaptic Plasticity	60	Mild	ß2-AR agonist	Oral	NCT05104463
AbbVie (Syndesi acquisition)	ABBV 552	ABBV 552	Phase II		50-90	Synaptic Plasticity	240	Mild	SV2A Modulator	Oral	NCT05771428
CuraSen	CST 2032 (Clenbuterol)	CST 2032 (Clenbuterol)	Phase II		50-85	Synaptic Plasticity	60	Mild	ß2-AR agonist	Oral	NCT05104463
Cognition Therapeutics	CT 1812	CT 1812	Phase II		50-85	Synaptic Plasticity	540	Early	Sigma-2/PGRMC1 antagonsit	Oral	NCT05531656
Cognition Therapeutics	CT 1812	CT 1812	Phase II		50-85	Synaptic Plasticity	378	Mild-to-moderate	Sigma-2/PGRMC1 antagonsit	Oral	NCT03507790
ReST Therapeutics	FluoroEthylNorMemantine	FluoroEthylNorMemantine	Phase I		18-45	Synaptic Plasticity	36	Healthy volunteers	NMDA receptor agonist	Oral	NCT05921929
Axoltis Pharma	NX210c	NX210c	Phase I		55+	Synaptic Plasticity	30	Healthy elderly volunteers	Thrombospondin replacements	IV	NCT05827653
Allyx Therapeutics/Bristol-Myers Squibb	ALX-001 / BMS-984923	ALX-001 / BMS-984923	Phase I		50-80	Synaptic Plasticity	50	Healthy volunteers Mild (Part II)	Glutamate modulator (mGluR5)	Oral	NCT05804383
Allyx Therapeutics/Bristol-Myers Squibb	ALX-001 / BMS-984923	ALX-001 / BMS-984923	Phase I		50-80	Synaptic Plasticity	12	Healthy volunteers Mild (Part II)	Glutamate modulator (mGluR5)	Oral	NCT05817643
Anavex	Anavex 3-71	Anavex 3-71	Preclinical			Synaptic Plasticity			OPRS1 agonist + M1 muscarinic activator (positive modulator)	Oral	

Source: Bloomberg Intelligence

Figure 28: Inflammation Modulators Pipeline

Company	Drug	Drug Profile	Phase	Trial name	Age group studied	General Mechanism	Enrollment	Patient Population	Modality	Mode of Admin.	NCT Number
Inflammation											
Tiziana Life Sciences	Foralumab	Foralumab	Phase II			Inflammation		Early	CD3 monoclonal antibody	Intranasal	
Inmune Bio	Pegipanermin	Pegipanermin	Phase II	OLE-XPro1595	55-85	Inflammation	261	Mild	sTNF-alpha Inhibitor	SC	NCT05522387
Inmune Bio	Pegipanermin	Pegipanermin	Phase II	MINDFul	60-85	Inflammation	201	Mild	sTNF-alpha Inhibitor	SC	NCT05318976
Novartis	Canakinumab	Canakinumab	Phase II		45-90	Inflammation	34	Mild	IL-1ß inhibitor	SC	NCT04795466
TrueBinding	TB006	TB006	Phase II		50+	Inflammation	180	Early	TIM-3 monoclonal antibody	IV	NCT05476783
Alector/AbbVie	AL 002	AL 002	Phase II	INVOKE-2	50-85	Inflammation	328	Early	TREM2 monoclonal antibody	IV	NCT04592874
Alector/AbbVie	AL 002	AL 002	Phase II	AL002-2 LES	50-85	Inflammation	210	Early	TREM2 monoclonal antibody	IV	NCT05744401
Vigil Neuroscience	VG-3927	VG-3927	Preclinical			Inflammation			TREM2 monoclonal antibody	Oral	
Hoth Therapeutics	HT ALZ	HT ALZ	Preclinical			Inflammation			substance P/neurokinin-1 receptor modulator	Oral	
Ventyx Biosciences	VTX 3232	VTX 3232	Preclinical			Inflammation			NLRP3 inhibitor	Oral	

Source: Bloomberg Intelligence

Figure 29: Other Mechanisms Pipeline

Company	Drug	Drug Profile	Phase	Trial name	Age group studied	General Mechanism	Enrollment	Patient Population	Modality	Mode of Admin.	NCT Number
Other											
Novo Nordisk	Semaglutide	Semaglutide	Phase III	EVOKE	55-85	Other	1840	Early	GLP-1 Agonist	Oral	NCT04777396
Novo Nordisk	Semaglutide	Semaglutide	Phase III	EVOKE-Plus	55-85	Other	1840	Early	GLP-1 Agonist	Oral	NCT04777409
Novo Nordisk	Semaglutide	Semaglutide	Phase III		55-75	Other	24	Mild	GLP-1 Agonist	Oral	NCT05891496
Cerecin	Tricaprilin	Tricaprilin	Phase III	Phase 3 AD	50-80	Other	535	Mild	Ketone body stimulant	Oral	NCT05809908
Partner Therapeutics	sargramostim	sargramostim	Phase II	SESAD	60-80	Other	42	Mild-to-moderate	GMC stimulating factor	SC	NCT04902703
Neurokine Therapeutics	MW150	MW150	Phase II	SKI-AD	50-90	Other	24	Mild-to-moderate	Stress Kinase Inhibitor	Oral	NCT05194163
Stemedica Cell Technologies	hMSCs	hMSCs	Phase II		55-80	Other	40		Human MSCs	IV	NCT02833792
Longeveron	Lomecel-B	Lomecel-B	Phase II	CLEARMIND	60-85	Other	48	Mild	Allogeneic MSC	IV	NCT05233774
Beijing Joekai Biotechnology	50561	50561	Phase II		50-85	Other	60	Mild-to-moderate	Rac1 inhibitor	Oral	NCT05811442
Nature Cell Co	AstroStem	AstroStem	Phase II		50+	Other	100		Autologous adipose MSCs	IV	NCT04482413
NeuroSense Therapeutics	PrimeC	PrimeC	Phase II	RoAD	55-85	Other	20	Mild-to-moderate	Topoisomerase inhibitor	oral	NCT06185543
VT Bio/MediForum	PM 012	PM 012	Phase II	PM012-2b	50-85	Other	312	Mild	Herbal-based derivative	Oral	NCT05811000
GemVax	GV1001	GV1001	Phase II		55-85	Other	180	Mild-to-moderate	Immunostimulant peptide vaccine	SC	NCT05189210
Janssen/Minerva Neurosciences	Seltorexant	Seltorexant	Phase II		55-85	Other	86	Early	Hypocretin-receptor antagonsit	Oral	NCT05307692
Treeway	TW001	TW001	Phase II	ASURE	55-80	Other	60	Early-to-mild	Free radical scavenger	Oral	NCT05323812
IntelGenX	Montelukast	Montelukast	Phase II	BUENA	50+	Other	54	mild-to-moderate	Leukotriene D4 antagonist	Oral	NCT03402503
Medesis Pharma	NP03	NP03	Phase II	NanoLi_AD	50-90	Other	68	Mild-to-severe	Lithium therapy	Oral	NCT05423522
reMYND	REM0046127	REM0046127	Phase II		50-85	Other	60	Mild-to-moderate	Calcium homeostasis	Oral	NCT05478031
Cyclo Therapeutics	Trappsol Cyclo	Trappsol Cyclo	Phase II	EAD501	50-80	Other	90	Mild-to-moderate	Cholesterol modulator	IV	NCT05607615
GlaxoSmithKline	GSK4527226	GSK4527226	Phase II	PROGRESS-AD	50-85	Other	282	Early	SORT1 inhibitor	IV	NCT06079190
Excelsior	EX039	EX039	Phase II		50-80	Other	120	Mild	Ammonia scavenger	Oral	NCT05413655
Vaccinex	Pepinemab	Pepinemab	Phase I/II	SIGNAL-AD	55-85	Other	50	Mild-to-moderate	CD100 monoclonal antibody	IV	NCT04381468
Denali Therapeutics/Takeda	TAK-594 (DNL593)	TAK-594 (DNL593)	Phase I/II		18-80	Other		Healthy volunteers and FTD patients	Progranulin replacement	IV	NCT05262023
CHABiotech CO., Ltd	CB-AC-02	CB-AC-02	Phase I/II		50+	Other	24	Early-to-Mild	Human placenta MSCs	IV	NCT02899091
NKGen	SNK01	SNK01	Phase I/II		40-85	Other		Mild	Autologous NK cell replacement	IV	NCT06189963
Eisai	E-2025	E-2025	Phase I		18-55	Other		Healthy volunteers	EphA4 modulator	IV	NCT05726851
Regeneration Biomedical	RB-ADSC	RB-ADSC	Phase I		45-80	Other	18	Mild-to-moderate	Autologous adipose-derived stem cells	IV	NCT05667649
NKGen	SNK01	SNK01	Phase I	ASK-AD	55-85	Other	30	Mild	Autologous NK cell replacement	IV	NCT04678453
Immunobrain Checkpoint	IBC Ab002	IBC Ab002	Phase I		50-80	Other	40	Early	PD-L1 monoclonal antibody	IV	NCT05551741
Perha Pharmaceuticals	Leucettinib-21	Leucettinib-21	Phase I	LEUCETTA	18-45	Other	120		DYRK1A kinase inhibitor		NCT06206824
Artery Therapeutics	CS 6253	CS 6253	Phase I		18-80	Other	64	Healthy volunteers and APOe4 carriers	ABCA1 agonist	IV	NCT05965414
Roche	RG-6289	RG-6289	Phase I			Other			Undisclosed		
Coya Therapeutics	COYA-301	COYA-301	Preclinical			Other			IL2-based T-Reg Activator	SC	
VT Bio	VT 301	VT 301	Preclinical			Other			T-reg therapy		

Source: Bloomberg Intelligence

Section 14. Model Output

Figure 30: Risk Adjusted Global Scenario Output

Net Revenue (k$ - Risk Adjusted)	2021 Dec-21	2022 Dec-22	2023 Dec-23	2024 Dec-24	2025 Dec-25	2026 Dec-26	2027 Dec-27	2028 Dec-28	2029 Dec-29	2030 Dec-30
Alzheimer's therapies										
Leqembi (lecanemab)	-	-	12,500	192,137	652,213	1,426,512	1,746,985	2,880,785	3,288,567	3,934,061
Donanemab	-	-	-	60,713	404,724	972,180	1,578,240	2,846,942	3,846,437	4,590,815
Aduhelm (aducanumab)	3,045	4,800	27,104	-	-	-	-	-	-	-
Remternetug	-	-	-	-	-	234,156	648,100	1,374,824	1,949,852	2,520,425
Valiltramiprosate	-	-	-	-	79,276	183,918	313,404	474,126	598,723	731,602
Simufilam	-	-	-	-	-	124,422	236,652	410,489	530,601	640,900
ACI.24.060	-	-	-	-	-	-	-	76,144	145,590	293,741
TOTAL	**3,045**	**4,800**	**39,604**	**252,850**	**1,073,460**	**2,941,188**	**4,523,381**	**8,063,311**	**10,359,770**	**12,711,543**

Source: Bloomberg Intelligence

Figure 31: Unadjusted Output

Net Revenue (k$)	2021 Dec-21	2022 Dec-22	2023 Dec-23	2024 Dec-24	2025 Dec-25	2026 Dec-26	2027 Dec-27	2028 Dec-28	2029 Dec-29	2030 Dec-30
Alzheimer's therapies										
Leqembi (lecanemab)	-	-	12,500	203,437	621,720	1,334,993	1,835,736	2,897,734	3,475,135	4,031,891
Donanemab	-	-	-	70,027	466,809	1,005,975	1,820,346	3,040,794	5,229,438	6,144,810
Aduhelm (aducanumab)	3,045	4,800	27,104	-	-	-	-	-	-	-
Remternetug	-	-	-	-	-	476,980	1,408,914	2,479,854	3,416,823	4,103,858
Valiltramiprosate	-	-	-	-	178,200	414,473	709,152	1,084,160	1,371,058	1,670,348
Simufilam	-	-	-	-	-	270,483	514,462	892,368	1,153,481	1,393,260
ACI.24.060	-	-	-	-	-	-	-	313,313	580,205	831,358
TOTAL	**3,045**	**4,800**	**39,605**	**273,463**	**1,266,729**	**3,502,905**	**6,288,609**	**10,708,223**	**15,226,140**	**18,175,526**

Source: Bloomberg Intelligence

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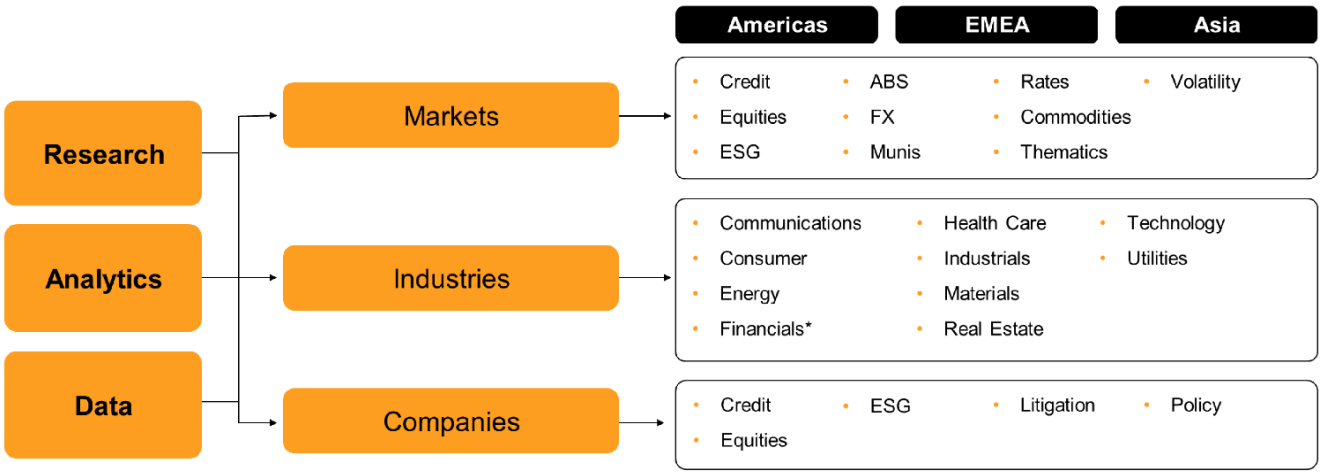

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