AlphaSense

A Transformative Era for Alzheimer's Treatments

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A Transformative Era for Alzheimer’s Treatments

Executive Summary

FDA approval of Leqembi by Eisai and Biogen represents a transformative milestone in Alzheimer's disease treatment, offering the first drug to fundamentally slow cognitive decline. Eli Lilly's donanemab has also proven to slow Alzheimer’s progression and is poised for FDA approval in early 2024.

The Alzheimer's market, affecting 6.7 million Americans, is poised to double by 2050, underscoring the need for effective treatments. Nevertheless, Leqembi’s commercial launch has been restrained by a lengthy patient identification process, severe adverse events, complex infusion administration, and inadequate rollout communication. Meanwhile, the clinical success of Leqembi and donanemab has reignited investment in Alzheimer's drug development, with a record number of clinical trials in the pipeline.

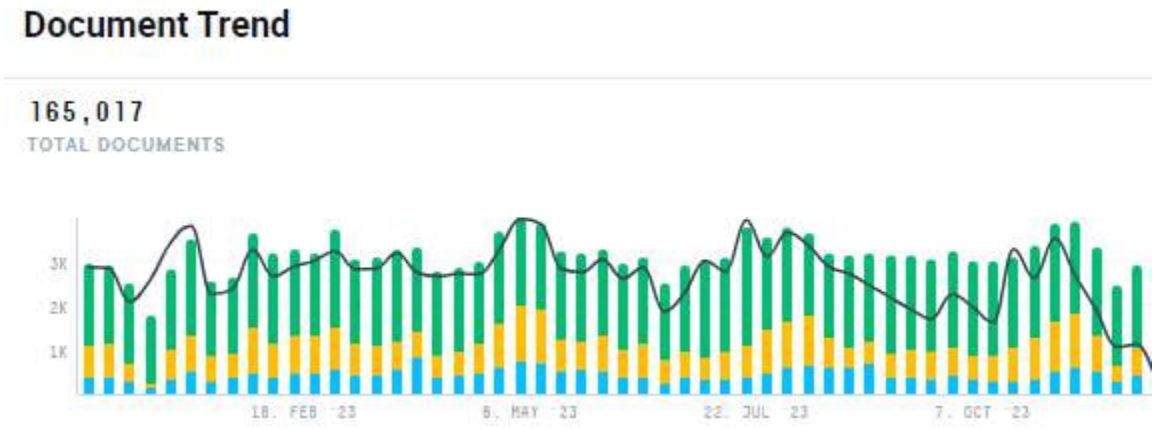
In the short term, market observers are focused on Leqembi’s ability to overcome adoption barriers and the upcoming launch of donanemab. Beyond that, experts say the industry is poised for continued innovation, with hopes pinned on early Alzheimer’s intervention and prevention, combination therapies, and the eventual transformation of Alzheimer's disease from a devastating reality into a distant memory.

New Drugs Break Through

FDA approval of Eisai and Biogen's Leqembi earlier this year ushered in what many are calling a transformative era in the treatment of Alzheimer's disease, the most common form of dementia. After decades of failed attempts, Leqembi broke through to become the first drug to slow the cognitive decline characteristic of Alzheimer's, and, unlike previous drugs, Leqembi acts on a fundamental mechanism of the disease rather than simply treating disease symptoms.

> "Leqembi is actually… disease-modifying. It's not just treating the symptoms. It's not just cutting the weeds. It's pulling them [out] from the ground."
>
> **– Neurologist | Expert Transcript**

Building on the momentum is Eli Lilly's donanemab, which proved to slow cognitive decline in clinical trials and is expected to receive FDA approval in Q1 of 2024. In addition, researchers are performing a record number of clinical trials in the Alzheimer's domain.

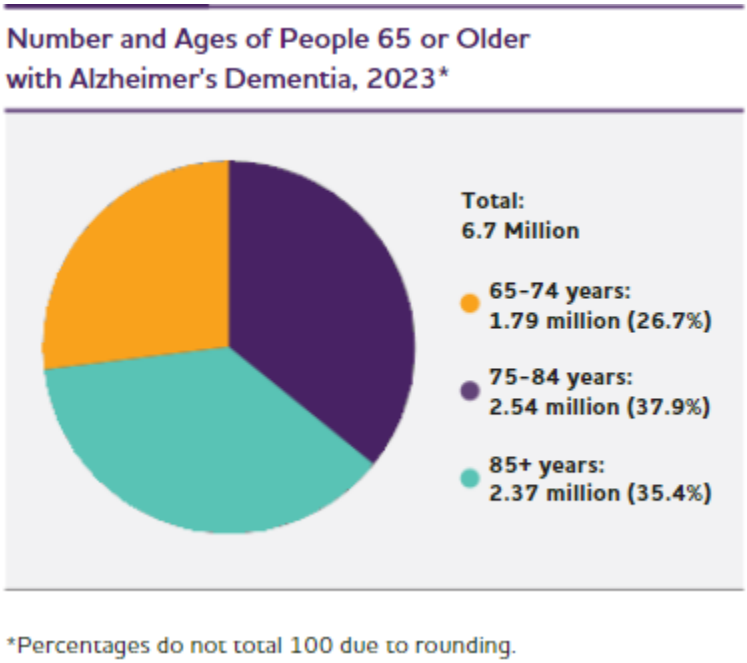


Source: AlphaSense

The number of documents mentioning Alzheimer's disease within the AlphaSense platform has remained strong during the past year, reflecting enthusiasm about the new Alzheimer's treatment landscape. Let's explore this topic and its key debates by leveraging AlphaSense, including first-person insights from our expert transcript library.

Huge Addressable Market

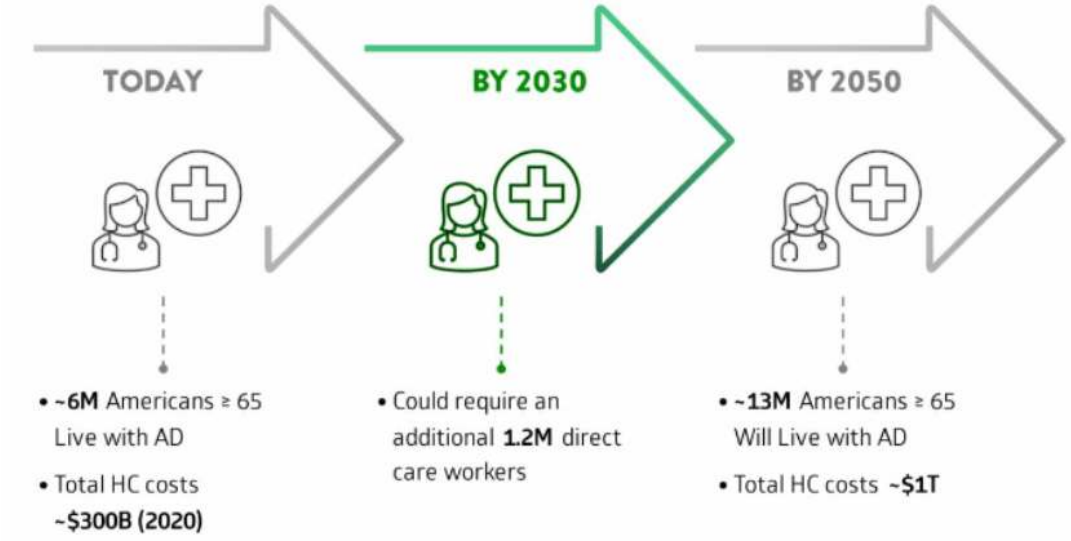
Alzheimer's disease is both devastating in its effects and broad in its reach. Approximately 6.7 million- or one in nine -Americans 65 and older are living with Alzheimer's, and incidence of the disease increases with age.



Source: Alzheimer's Association

As the population ages, the number of Americans 65 and older with Alzheimer's is expected to more than double by 2050, while associated healthcare costs are expected to more than triple. This scenario will likely require an influx of direct care workers in an already tight labor market as roughly 75% of Alzheimer's patients 80 years old and above live in a nursing home compared with 4% among the general population. In addition, Alzheimer's is the fifth leading cause of death among Americans 65 and older.

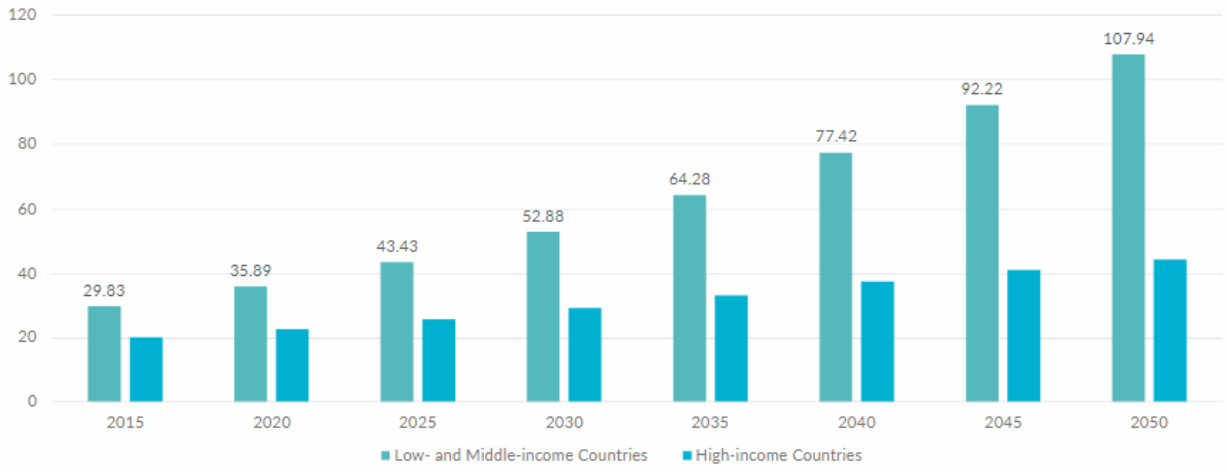
U.S. Alzheimer's Disease Cases and Costs Expected to More Than Double



Source: TD Cowen, Alzheimer's Association

Globally, more than 55 million people were living with Alzheimer's and other forms of dementia during 2020. This figure is expected to rise to 139 million by 2050 and grow relatively faster among populations in low- and middle-income countries. Caregivers are also affected, with 50% of caregivers globally reporting health impacts due to their responsibilities, even while expressing positive sentiments about their role.

Millions of People With Dementia in Low- to High-Income Countries, 2015-2050



Source: Mordor's Intelligence, Alzheimer's Disease International

Although Alzheimer's treatments- both on the market and in development -clearly have a large and critical market opportunity, numerical estimates are scarce because visibility is limited to factors such as regulatory approvals, adoption curves, pricing, and reimbursement.

Furthermore, numerical forecasts that do exist vary widely. For instance, Sanford Bernstein forecast the market for Alzheimer's treatments to reach $30B-$40B by 2035, while HSBC projected the market in the U.S. alone to exceed $50B by 2030.

Results Quiet Amyloid Debate

Leqembi and donanemab are both antibodies designed to remove sticky deposits of a protein called amyloid beta, which is toxic to brain cells and eventually causes brain cells to die. Both drugs aim to slow Alzheimer's progression in patients who are in the early stage of the disease, which is marked by mild cognitive impairment.

In clinical trials lasting 18 months, Leqembi slowed cognitive decline in early-Alzheimer's patients by 27%, while donanemab slowed decline by 35%. The efficacy difference may be explained by how the two drugs target amyloid protein. Leqembi targets amyloid as it begins to form fibers, while donanemab binds to amyloid once fibers have clumped together to form larger plaques.

The cognitive benefits are generally considered modest, but these drugs have quieted a decades-long debate about whether removing amyloid protein affects cognition in Alzheimer's patients at all. The debate was fueled by dozens of failed anti-amyloid drug trials and came to a head after the FDA's controversial 2021 decision to approve Biogen's Aduhelm treatment, even though amyloid plaque reduction achieved in trials did not translate into cognitive benefits. (The Centers for Medicare and Medicaid Services (CMS) eventually restricted Aduhelm coverage, which stifled Aduhelm's commercial prospects.)

Now that Leqembi and donanemab have bolstered confidence in amyloid-targeting therapy, the debate has shifted to the commercial rollout of Leqembi (following full FDA approval in July) and the eventual rollout of donanemab.

Slow Adoption of Leqembi Despite Patient Interest

AlphaSense industry experts report strong patient interest in the new anti-amyloid treatments or anticipate strong interest as word spreads.

> "Most people will do anything they can as far as a proper [Alzheimer's] diagnosis and treatment because it's such a life-shattering… disease."
>
> **– Geriatrician | Expert Transcript**

However, physician reaction is generally more cautious, with experts noting several issues limiting Leqembi uptake, at least initially.

> "Enthusiasm from patient and patient advocacy communities will probably exceed that of many clinicians because there's often less of a robust understanding [among patients] of the nuances of the risks."
>
> **– Neurologist | Expert Transcript**

Experts' relatively muted feedback on Leqembi uptake aligns with Eisai's recent earnings report, which posted weaker-than-expected Leqembi sales during FY2Q24 (July-September). However, the company maintained adoption is on track to achieve FY4Q24 (January-March) targets.

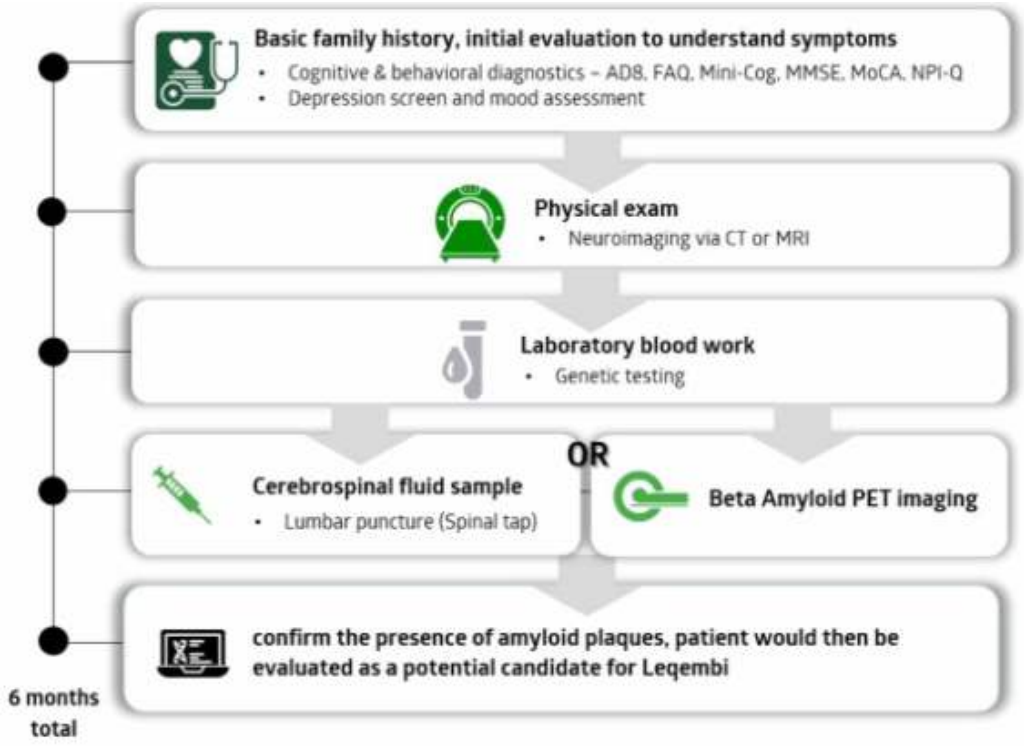
> "Leqembi sales of ¥400mn reported when announcing 2Q results struck us as a slow start, but management seemed confident in achieving its target of 10,000 patients by March."
>
> **– Bank of America | Report**

Experts said adoption hurdles fall into four main categories, we explore each hurdle in greater detail below.

Patient Identification

The process for identifying Leqembi patients is lengthy and requires multiple steps.

Steps In Alzheimer's Disease Diagnosis



Source: TD Cowen

Perhaps most onerous is the requirement for either positron emission tomography (PET) brain imaging or a cerebrospinal fluid (CSF) sample to confirm the presence of amyloid buildup in the brain, although CMS's October decision to better cover Alzheimer's diagnostic PET scans has eased the financial burden.

Compared with PET scans and CSF samples, blood-based tests are considered a better option in terms of cost and scalability. Labcorp, C2N, and Quanterix launched blood-based tests this year, all of which must be ordered through a healthcare provider. Quest also introduced a blood-based test, but unlike the others, Quest's is a direct-to-consumer test.

Whatever the model, experts generally believe these tests are not yet accurate nor affordable enough to be widely used.

> "The problem with the blood tests is that they're not covered by insurance, so they cost hundreds of dollars… [And] there's no aftermarket statistics as to how valuable the blood work is going to be. I don't know if it's [going to take] one year or 10… to know how valuable that information is head-to-head with a PET scan or a spinal tap."
>
> **– Neurologist | Expert Transcript**

Risk of Severe Adverse Events

Anti-amyloid treatments introduce the risk of a severe set of adverse events called amyloid-related imaging abnormalities (ARIA). The effects of ARIA can be asymptomatic (detected via brain imaging), result in brain swelling or bleeding, and even cause death in rare cases. These effects earned Leqembi an FDA black box warning, the agency's most stringent safety precaution. In clinical trials, 21% and 37% of Leqembi and donanemab patients, respectively, developed ARIA.

Both the cause and treatment of ARIA are not yet understood well, which has made physician experts cautious about the treatment.

> "Given the risk, I just don't think that, right now, we're where we need to be. I wouldn't feel comfortable prescribing this."
>
> **– Neurologist | Expert Transcript**

Some experts said ARIA is the biggest hindrance to Leqembi use.

> "I'm still learning about what the incidence is for ARIA in different patient populations, but that's the one [thing] that would make me hesitate [before] using [Leqembi] because patient safety is first and you want to first do no harm."
>
> **– Neurologist | Expert Transcript**

Leqembi requires regular MRI monitoring to manage ARIA risk, as will donanemab.

Infusion Administration

The new anti-amyloid drugs require administration via IV infusion– bi-weekly for Leqembi and monthly for donanemab. According to experts, infusion requirements along with MRI monitoring create a demanding and costly treatment schedule for patients.

> "[Leqembi adoption] is going to be a matter of patient willingness and ability to deal with the cost and the burden of having all these appointments."
>
> **– Geriatrician | Expert Transcript**

Rollout Communication

Complicating matters, some experts said communication about Leqembi's rollout and protocols has been insufficient for both patients and providers alike.

> "There's a lot of confusion on what are the actual steps [to get patients on Leqembi]. I think you've got to do a lot of research to understand what the steps are… Is your doctor even aware? Many of them are not. They don't understand the rollout."
>
> **– Social Worker | Expert Transcript**

This expert said another source of uncertainty is out-of-pocket costs for Leqembi, which is priced at $26,500 per year before insurance coverage.

> "The majority of the people who have any form of this disease are not wealthy. We just had the recent approval for [Leqembi] to be covered by Medicare, and it might be covered by Medicaid or the VA… It's not necessarily easy for people to access [information about] these things."
>
> **– Social Worker | Expert Transcript**

Eisai estimates that 91% of patients will pay nothing for Leqembi or a few dollars per day, thanks to Medigap supplemental insurance, Medicare Advantage, Medicaid, or commercial insurance coverage. However, nine percent of patients would still be on the hook for the 20% copay required by traditional Medicare, which could run this group more than $5,000 per year. Eisai said it has implemented a patient assistance program to ease such costs.

Leqembi vs. Donanemab: Too Soon to Call

With donanemab on track to receive FDA approval during Q1 of 2024, the investment community is focused on what effect this will likely have on Leqembi's market share. Most experts who commented on the two treatments did not have strong preferences either way but instead expressed opinions about the anti-amyloid class as a whole.

> “I wouldn't say I'm more excited about one than the other. I think they both have problematic side effects and monitoring [requirements] that are barriers.”
>
> **– Geriatrician | Expert Transcript**

Other experts said more information about donanemab is needed before making comparisons.

> “Lecanemab has already been approved for everything, and donanemab is only going through the process. We don’t know the entire story about donanemab yet.”
>
> **– Drug Discovery Scientist | Expert Transcript**

Pipeline Momentum

The new wave of anti-amyloid drugs has reinvigorated investment in Alzheimer’s drug development. As of January 1, 2023, there were 187 clinical trials assessing 141 unique treatments in the Alzheimer’s pipeline, nearly matching the previous year’s record level of 143 unique treatments.

The pipeline consists of anti-amyloid drugs in different formulations as well as drugs that target different disease mechanisms altogether, which could facilitate combination therapies.

> “Alzheimer’s is going to be like cancer. Cancer is not a one-shot disease… You attack cancer in multiple ways for it to get into remission. It's the same with neurodegenerative diseases, at least initially. Once [patients] are diagnosed, you can't expect the disease to be arrested only by amyloid.”
>
> **– Drug Discovery Scientist | Expert Transcript**

We explore the pipeline highlights in greater detail below.

Subcutaneous Formulations

Biogen and Eisai are collaborating on a subcutaneous (or injectable) form of Leqembi, which posted successful data in October showing 14% more amyloid plaque cleared than the current IV formulation with no additional ARIA risk. Notably, the weekly Leqembi injection would allow patients to receive the drug at home instead of traveling to an infusion center twice a month.

Subcutaneous Leqembi could be on the market by early 2025 if all goes according to the plan. Meanwhile, Lilly is developing a second-generation amyloid-targeting drug, remternetug, that has the potential for subcutaneous delivery.

Alzheimer's Vaccines

There are a number of Alzheimer's vaccines under development, including ABvac40 from Araclon Biotech (part of Grifols), which recently demonstrated a 38% slowdown in disease progression by targeting amyloid beta.

> "The appeal is that, with the [AVvac40] vaccine, you're having a patient's biological immune system generate a natural response as opposed to injecting the patient with pre-formed antibodies, which over time may wane quicker than antibodies the patient generates himself… [And] there's no ARIA reported, which suggests this vaccine may be safer and more cost-effective [than Leqembi and donanemab]."
>
> **– Neurologist | Expert Transcript**

Other companies developing Alzheimer's vaccines include Vaxxinity, AC Immune, and Prothena.

Amyloid Precursor Protein

Alnylam and Regeneron are collaborating on a drug that targets amyloid precursor protein or APP, which could prevent amyloid buildup to begin with.

> "This is a novel, interesting approach…It's trying to prevent [amyloid beta], rather than remove it… It's very exciting."
>
> **– Neurologist | Expert Transcript**

Tau-Targeting Drugs

Researchers are also targeting a separate Alzheimer's protein called tau, which also builds up in the Alzheimer's brain and creates tau tangles that interfere with brain activity. Much is still unknown about the relationship between amyloid beta and tau, but many researchers believe both must be addressed to advance Alzheimer's treatments.

> "There is also attention, more recent if you [will], toward the tau protein…You can have a brain that has amyloid plaques; nevertheless, the person never had clinical signs of Alzheimer's. This tells us that.. we need to be proactive and keep an eye on other possibilities as well."
>
> **– Clinical Neurologist | Expert Transcript**

Companies pursuing tau drugs include Biogen, Eisai, Lilly, and Roche. In addition, Bristol Myers Squibb purchased global commercial rights for Prothena's PRX005 anti-tau candidate earlier this year.

Looking Ahead

AlphaSense will continue to publish first-person expert insights that monitor developments in the Alzheimer's treatments market.

In the short term, all eyes will be on Eisai and Biogen's ability to accelerate Leqembi adoption, requiring physicians to overcome ARIA concerns, faster patient identification, and improved rollout communication. Donanemab's launch and its impact on Leqembi's market position will also be in focus, as will the FDA's response to Eisai's expected late-Q1 application for subcutaneous Leqembi approval.

Further out, market observers will follow which pipeline treatments break through to build on the recent success of the new anti-amyloid treatments. Meanwhile, blood-based diagnostic tests will need to make serious strides to support market growth.

In the longer term, experts believe the shift to earlier intervention- even prevention -of this devastating disease will continue, and they anticipate a future where combination therapies target multiple Alzheimer's mechanisms. Ultimately, the new treatment landscape has ignited hopes that one day, Alzheimer's disease will be but a distant memory.

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