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Illuminating the Road Less Traveled in Biotech: Radiopharmaceuticals – Fourth Edition

Focus on Alzheimer's Disease Imaging

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Introduction

We believe the radiopharmaceutical industry represents one of the most compelling secular growth opportunities in biotech in the next three to five years. Defying the conventional belief that it remains a niche market, we are optimistic that the recent resurgence in investor and big pharma interest that culminated in four high-profile acquisitions (Point Biopharma by Eli Lilly, RayzeBio by Bristol Myers, Fusion Pharma by AstraZeneca, and Mariana Oncology by Novartis), coupled with Novartis's recent increase in Pluvicto peak sales guidance (to $5 billion, from $3 billion previously), will continue to drive investment in the field. In 2025, radiopharma companies received roughly $900 million in private financings.

It is our aim to provide a yearly update on radiopharmaceuticals to serve as a resource for investors who would like to gain knowledge and understanding in this rapidly evolving space that has attracted a significant inflow of investment. Our first edition (see: Bioluminescence—Illuminating the Road Less Traveled in Biotech: Radiopharmaceuticals) provided an in-depth analysis of the field at large, and we refer readers to that report for a historical background on the field and fundamental nuclear chemistry concepts. In our second edition (see: Illuminating the Road Less Traveled in Biotech: Radiopharmaceuticals – Second Edition), we focused on elucidating the supply chain portion of the industry, given that we view this as one of the more obscure and difficult-to-understand and -visualize areas. We also provided an in-depth overview of the various medically relevant radioisotopes that are being explored for therapeutic applications, a description of current and future trends, and a comprehensive list of radiopharmaceutical companies in both the therapeutic and diagnostic fields, though in general focused our discussion on the therapeutic application. In the third edition (see: Illuminating the Road Less Traveled in Biotech: Radiopharmaceuticals – Third Edition), we provided a brief update on the radiopharmaceutical field, including recent financing, the current company landscape, clinical updates, and targets of interest (again focusing on the therapeutic aspect of the industry).

In the current edition, we take a departure from the therapeutic landscape and focus instead on the role of diagnostics. Given that the PET imaging market is a promising area of growth for radiopharmaceuticals, in our view, we aim to elucidate the evolving role of PET in the context of diagnosing Alzheimer's disease. We believe this application represents a material use-case for radiopharmaceuticals beyond oncology and provides an example of the diagnostic power of medically relevant radioisotopes. Although PET is being evaluated for neurodegenerative disease beyond Alzheimer's disease, we focus on those developed for Alzheimer's disease given that tracers for other pathologies are less well established.

Background on Alzheimer's Disease

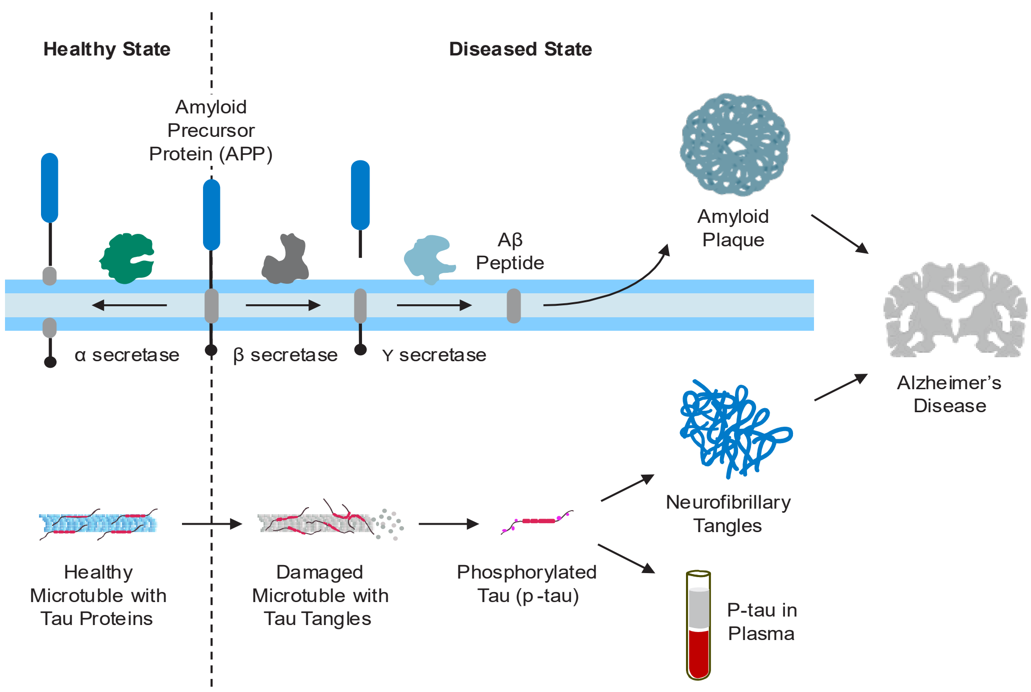
Alzheimer's disease is the most common form of dementia, accounting for 60%-70% of all dementia cases. According to the Alzheimer's Association, more than 7 million Americans are living with Alzheimer's disease; the majority (74%) are 75 years of age or older. It is estimated that roughly 11% of adults 65 years or older have Alzheimer's disease, and women constitute roughly two-thirds of all Alzheimer's disease occurrences. Cases continue to climb, and by 2050, nearly 13 million Americans could be living with Alzheimer's disease (though this estimate could be reduced pending effective cures or preventive therapies). Alzheimer's disease has been identified as the seventh-leading cause of death in the United States. The direct healthcare costs associated with treatment for Alzheimer's patients are estimated to be nearly $384 billion in 2025 and are expected to reach nearly $1 trillion over the next 25 years.

Beyond age and gender, genetics (*APOE* in particular) is an important risk factor for Alzheimer's. While *APOE ε2* (occurring in 5%-10% of the population) potentially provides protection against the disease, *APOE ε4* (present in 15%-25%, though only 2%-5% have two copies) appears to increase the risk of developing Alzheimer's disease, especially when two copies are present. Since *APOE ε4* is also a risk factor for developing amyloid-related imaging abnormalities (ARIA; a side effect of anti-amyloid therapies), the label for Leqembi suggests that *APOE ε4* testing be carried out before initiating treatment to help determine a patient's risk for developing ARIA. Given these associations, there is potential for the field to move toward routine genetic screening to identify patients who could benefit from initiating earlier treatment.

Alzheimer's Disease Pathology

Cognitive decline associated with Alzheimer's disease results from two classes of abnormal structures in the brain: amyloid plaques and neurofibrillary tangles (also known as NFTs). These structures are densely packed filaments of amyloid-beta peptides and tau proteins, respectively (exhibit 1). They accumulate in the brain and are correlated with cell death, tissue loss, and consequential cognitive decline. Amyloid plaques form between neurons when amyloid-beta peptides (which are snipped from the amyloid precursor protein by an enzyme) are not efficiently cleared from the brain. These peptides are said to be "sticky," which contributes to clumping. The clumps and plaques that form can block synapses and prevent signaling between cells. In some cases, they can also activate an inflammatory immune response that leads to neuron death.

Exhibit 1
Radiopharmaceuticals
Pathophysiological Changes Associated With Alzheimer's Disease



Source: Lai, R. et al. *Biomedicines* (2024)

NFTs contribute to cognitive decline in a different manner. In healthy individuals, tau proteins help form microtubules that transport nutrients within nerves in the brain. However, in patients with Alzheimer's disease, these microtubules break down, and the "free" tau proteins stick together due to their hyperphosphorylated state. The resulting aggregates are insoluble and are referred to as paired helical filaments, or PHFs. These filaments are the building blocks of NFTs. Without functional microtubules, the neurons are starved of nutrients, which can lead to nerve death through loss of axonal transport and blockage of nuclear transport. NFTs accumulate over the course of the disease and trigger cognitive decline. Unlike amyloid plaques, which can begin accumulating decades before cognitive symptoms are evident, NFTs become prominent when cognitive decline becomes apparent. Therefore, they are typically associated with the symptomatic stages of Alzheimer's disease and can provide a proxy for disease progression by comparing accumulation of NFTs over time.

Neurodegenerative diseases that are characterized by tau deposits in the brain are collectively referred to as tauopathies. Tauopathies are further classified based on the tau isoforms that are predominant in the aggregates. In humans, there are six brain-specific isoforms of tau: 0N3R, 0N4R, 1N3R, 1N4R, 2N3R, and 2N4R. Accordingly, tauopathies are classified as follows: 3R (mostly consisting of 3R tau), 4R (mostly consisting of 4R tau), and 3R/4R (containing roughly equal 3R and 4R). Some neurodegenerative disorders, such as Pick's disease (3R tauopathy), progressive supranuclear palsy (PSP, 4R tauopathy), and corticobasal degeneration (CBD, 4R tauopathy), are referred to as primary tauopathies since tau aggregates are the primary cause of the disease. However, other neurodegenerative disorders, such as Alzheimer's disease (3R/4R tauopathy), are classified as secondary tauopathies since the tau aggregates are not the primary cause of the disease but instead result from other pathology (amyloid-beta plaques in Alzheimer's disease, for example).

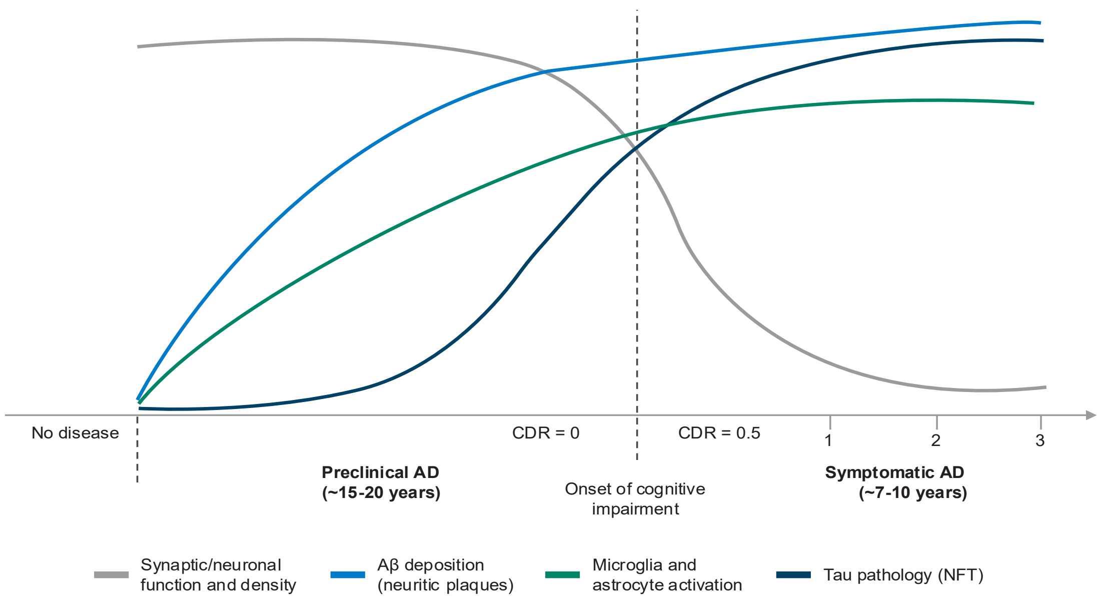
The degree of NFT pathology in patients with Alzheimer's disease can be described by the semi-quantitative Braak staging system. Severity ranges from Braak I to Braak VI with stages I and II referring to NFTs restricted to the transentorhinal cortex (early-stage disease), stages III and IV associated with limbic involvement (early-moderate stage), and stages V and VI including cases where NFTs have spread to the isocortical region (moderate-late stage). The Braak stages can be correlated with a B score, a system that is cited in Tauvid's label. A score of B0 indicates no NFT pathology, B1 is associated with Braak stages I and II, B2 refers to Braak stages III and IV, and B3 is linked to Braak stages V and VI. This system can provide a framework for staging patients and determining if a particular patient is "positive" or "negative" for Alzheimer's disease.

It is important to note that NFT pathology is a hallmark of cognitive disorders beyond Alzheimer's disease (e.g., frontotemporal dementia and PSP). Thus, a diagnosis of Alzheimer's disease requires proof of both amyloid plaques and tau tangles being present. However, some research suggests that tau tangles, and the presence of abnormal levels of certain aggregate-prone phospho-tau species (which can precede visible tau tangles), are a better marker for disease progression compared to amyloid plaques.

The occurrence of amyloid plaques and tau tangles can be analyzed through samples of cerebrospinal fluid (CSF) or PET scans of the brain. We also highlight that blood-based biomarkers can be used to indirectly analyze amyloid-beta and tau levels (this is discussed in more detail throughout the report).

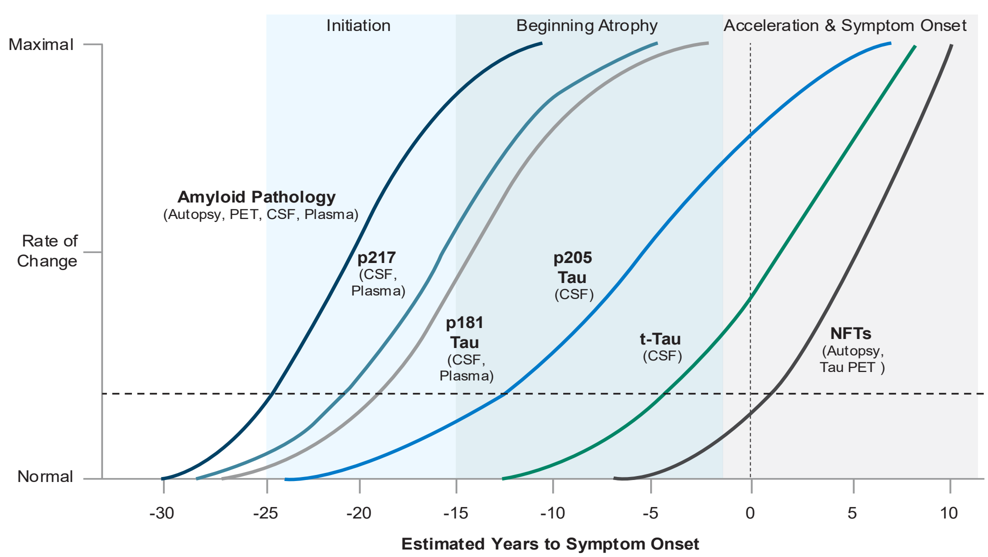
The process of developing Alzheimer's disease is slow. It can take 15 to 20 years before cognitive impairment is evident, and symptomatic Alzheimer's disease can take up to an additional 7 to 10 years to develop (exhibit 2). A number of biomarkers begin circulating in the blood or CSF long before disease onset. The first of these biomarkers is p-tau217, which is said to reflect both amyloid-beta and tau pathology and in some cases can be detected up to 20 years before symptoms occur (exhibit 3). This is followed by p-tau181, p-tau20, and t-tau. Analysis of NFTs, which can be detected by either autopsy or PET imaging, can typically only be carried out after symptom onset despite NFT pathology being present in relatively early stages of the disease.

Exhibit 2
Radiopharmaceuticals
Pathological and Clinical Changes Associated With Alzheimer's Disease During Disease Progression



NFTs=Neurofibrillary tangles
Source: Devi, G. *Front. Aging Neurosci.* (2023)

Exhibit 3
Radiopharmaceuticals
Changes in Biomarkers Associated With Alzheimer's Disease During Disease Progression

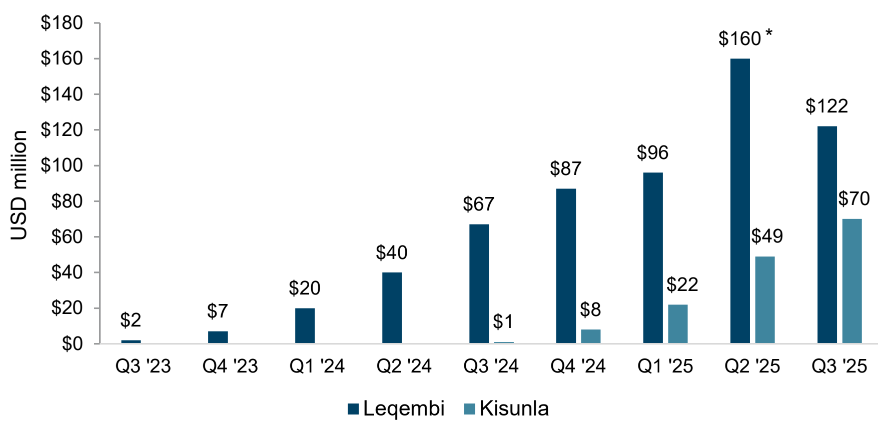


CSF=Cerebrospinal fluid
Source: Teunissen, C. et al. *Alzheimer's Dement.* (2025)

Treatment Landscape for Alzheimer's Disease

The treatment landscape for Alzheimer's disease has historically been met with material headwinds. In 2021, Aduhelm, a monoclonal antibody that targets amyloid-beta, was granted accelerated approval from the FDA. At the time, the approval marked a breakthrough moment given that it was the first drug approved for Alzheimer's disease since 2003 and was the first targeted treatment. However, in early 2024, Biogen announced that it was pulling Aduhelm from the market. Use of the therapy was limited due to what physicians viewed as lack of a clear clinical benefit (clinical trial data centered merely on reductions in amyloid-beta plaques) and the high cost of the treatment, especially given very limited insurance coverage. Another breakthrough in the field was marked by the recent approvals of next-generation anti-amyloid therapies, namely Eisai/Biogen's Leqembi, approved in 2023, and Eli Lilly's Kisunla, approved in 2024. Compared to Aduhelm, Leqembi and Kisunla have demonstrated a clearer positive impact on cognitive abilities (slowing of disease progression rather than just treating symptoms) and may be associated with superior safety profiles, particularly related to ARIA. Leqembi and Kisunla sales by quarter are presented in exhibit 4.

Exhibit 4
Radiopharmaceuticals
Sales of Leqembi and Kisunla by Calendar Quarter



*Impacted by $35 million of stockpiling in China.
Sources: Evaluate Pharma and William Blair Equity Research

Investigational therapies

Although there are currently few agents approved for treating Alzheimer's disease, there is continued interest in developing new therapies. A summary of approved or investigational therapies in company-sponsored pivotal trials for Alzheimer's disease is provided in exhibit 5, on the following page. The table includes biomarker and imaging criteria specified for enrollment.

Two pivotal trials that were closely watched, but ultimately failed, were the Phase III EVOKE and EVOKE Plus trials, which evaluated the potential for semaglutide to have a neuroprotective effect and aid in the treatment of early-stage symptomatic Alzheimer's disease. Of note, although semaglutide does not target amyloid beta, confirmation of amyloid pathology by PET or CSF analysis was still required. This is also true of several of the trials listed in exhibit 5. Therefore, we believe there is a potential use-case for amyloid beta PET imaging to serve as a broader diagnostic and screening tool.

Exhibit 5
Radiopharmaceuticals
Summary of Alzheimer's Disease (AD) Approved or Investigational Therapies in Pivotal Trials and Associated Eligibility Criteria

Drug Name	Mechanism of Action	Drug Sponsor	Trial ID	Biomarker Criteria	Imaging Criteria
Approved					
Leqembi	Anti-amyloid beta antibody	Biogen/Eisai	Phase II (NCT01767311) and Phase III (NCT03887455)	Positive amyloid-beta(1-42) CSF test[1]	Positive amyloid PET scan[1]
Kisunla	Anti-amyloid beta antibody	Eli Lilly	Phase III (NCT04437511)	Not specified	Positive amyloid and tau PET scan with Amyvid and Tauvid, respectively[2]
Aduhelm (pulled from market)	Anti-amyloid beta antibody	Biogen	Phase III (NCT02484547 and NCT024778000)	Amyloid-beta(1-42), p-tau, and t-tau CSF evaluated in substudies but not included in eligibility criteria	Positive amyloid PET scan
Investigational					
Remternetug	Anti-amyloid beta antibody	Eli Lilly	Phase III (NCT05463731)	Not specified	Positive amyloid PET scan
Buntanetap	Multiple neurotoxic protein inhibitor	Annovis	Phase III (NCT06709014)	Amyloid beta-positive (p-tau217 plasma level at screening)	AD diagnosis via MRI
ALZ-801	Amyloid oligomer formation inhibitor	Alzheon	Phase III (NCT04770220)	Not specified	Not specified[3]
Xanamem	Cortisol production inhibitor	Actinogen	Phase IIb/III (NCT06125951)	Plasma AD biomarker positive at pre-screening[4]	MRI negative for other diagnoses of dementia[4]
Gantenerumab	Anti-amyloid beta antibody	Roche	Phase III (NCT03444870 and NCT03443973) - both terminated	Positive tau/amyloid-beta42 CSF test[1]	Positive amyloid PET scan[1]
Simufilam	Altered filamin A binder	Cassava Sciences	Phase III (NCT04994483 and NCT05026177) - both terminated	Not specified[5]	Not specified[5]

[1]Requires one or the other to be positive.
[2]PET imaging can also provide a basis for patients to stop dosing if amyloid plaques are reduced to minimal levels.
[3]MRI showing abnormalities due to a condition other than AD is a key exclusion criteria.
[4]Can be one or the other or have a specified Clinical Dementia Rating or Mini-Mental State Examination score.
[5]Requires evidence of AD pathophysiology but does not specify the test.
Sources: Company reports and clinicaltrials.gov

Another approach under evaluation (though in earlier phases of development) is targeting TREM2, a protein that is expressed on myeloid cells and has been linked to neurodegenerative diseases, including Alzheimer's disease. Vigil Neuroscience (now part of Sanofi) is developing an oral small-molecule TREM agonist, VG-3927, that is Phase II ready. Compared to antibodies, the small-molecule format is said to have enhanced brain penetration, allowing for greater access to the target. Furthermore, the shorter half-life could allow for flexibility in dosing, especially if ARIA is observed. In May 2025, Sanofi announced a proposed acquisition of Vigil for $470 million to gain access to the asset (the acquisition was completed in August 2025). Sanofi had also been examining a Phase II antibody that targets TREM2, but the asset was returned to Amgen, perhaps because the small-molecule format appeared more promising. Regardless of the format, TREM2 has gained attention as a potential target for treating Alzheimer's disease.

Tau is also being investigated as a target for treating Alzheimer's disease. Biogen's BIIB080 is an antisense oligonucleotide therapy that received fast-track designation in April 2025 for the treatment of Alzheimer's disease. Phase Ib results demonstrated BIIB080's ability to decrease soluble tau in CSF and, based on PET measurements, decrease aggregated tau in the brain. The potential for improved clinical outcomes was also observed. The ongoing Phase II CELIA study is expected to be completed in May 2026, based on clinicaltrials.gov estimated timing. Eisai is investigating E2814 (also known as etalanetug), a tau-targeted antibody that is undergoing evaluation in the Phase II Study 202 trial, slated to be completed toward the end of 2026. A Phase II/III IST trial is also investigating E2814 in early-onset Alzheimer's caused by a genetic mutation with an expected completion in 2028. E2814 received FDA fast-track designation in September 2025. Other Phase II tau-targeted antibodies include Bristol Myers Squibb's BMS-986446 (specifically targets anti-MTBR tau and is under investigation in the Phase II TargetTau-1 trial) and UCB Biopharma's bepranemab (Phase II trial). Johnson & Johnson had been evaluating posdinemab in the Phase IIb AuTonomy trial, but the study did not meet its primary endpoint. Although using a slightly different modality, JNJ-64042056, which is a tau-targeted liposomal active immunotherapy/vaccine, is being investigated by Johnson & Johnson in the Phase II ReTain trial. Both of Johnson & Johnson's trials incorporated tau PET positivity in the enrollment criteria, and the primary endpoint for the E2814 trial is based on changes in tau PET. Therefore, it is our view that the use-case of tau PET is intertwined with the success of tau-targeted therapies.

The Role of Diagnostics

Requirement for treatment

A prerequisite for initiating treatment with either Leqembi or Kisunla is verifying the presence of amyloid-beta pathology. This is particularly important given that a quarter to a third of patients who meet the clinical criteria for Alzheimer's disease do not exhibit amyloid-beta pathology, which makes it difficult to identify candidates for amyloid-beta-targeting therapy based on clinical presentation alone. The presence of amyloid-beta pathology is typically confirmed with a CSF test or PET scan, though in some cases, plasma-based biomarkers can also be used (discussed in more detail below). Patient preference for the two most accepted methods varies; some prefer the less invasive nature of PET scans, while others opt for spinal taps due to accessibility, insurance coverage, and/or logistical considerations. For example, in some centers, PET scans are more logistically challenging and/or may not be available. On the other hand, not every center is equipped to analyze biomarkers in CSF. The label for Kisunla also recommends stopping treatment when amyloid-beta plaque levels rescind to minimal levels, which is assessed specifically with PET imaging. Therefore, we believe a use-case for PET imaging is in monitoring patient response to treatment.

Before the advent of amyloid-beta PET, FDG-PET was commonly used. FDG-PET can differentiate between many different dementias and neurodegenerative diseases but cannot elucidate the underlying disease pathology. Therefore, the use-case of FDG-PET is somewhat limited, though many neurologists still use this imaging method and believe it will continue to hold a place in diagnosis, especially given its affordable and easily available nature. In some cases, amyloid-beta PET scans can be negative yet FDG-PET still shows signs of neurodegeneration. Although not needed to initiate treatment, MRI is another imaging technique that is frequently used to monitor for ARIA, which cannot be detected with PET. In some practices, patients receive five to six MRI scans during their first year of treatment. While rates of ARIA can be as high as 30%-40% in clinical trials, physicians have observed a much lower rate of 10%-12% in the clinic.

The role of biomarkers

The Alzheimer's Association defines different categories of biomarkers by stage of disease. Based on revised criteria from 2024, core 1 biomarkers are defined as those appropriate for early detection of Alzheimer's disease (including both symptomatic and asymptomatic stages) and include Aβ42/40 and p-tau217/181/231 for CSF or plasma biomarkers and amyloid-beta PET for imaging. Core 2 biomarkers are those for later stages (including staging and predictions) and include MTBR-tau243, p-tau205, and non-phosphorylated tau fragments for CSF or plasma biomarkers (though non-phosphorylated fragments are typically only useful from CSF) and tau-PET for imaging. Core 2 biomarkers are more closely tied to onset of disease symptoms compared to core 1 biomarkers. The combination of core 1 and core 2 biomarkers can help in staging disease severity.

The expected change in a biomarker depends on the nature of the biomarker. For example, Aβ42/40 tends to decrease in patients with Alzheimer's disease due to accumulation in the brain and therefore a lower concentration in the CSF. In contrast, p-tau and t-tau tend to increase due to release of soluble forms of tau from neurons if they are dying (releasing p-tau) or degenerating (releasing t-tau). These changes in biomarker concentrations are readily measured in CSF. For the changes to be reflected in plasma, the biomarkers must pass the blood–brain barrier, which occurs to a limited extent. Therefore, changes in the plasma tend to be microscopic compared to the CSF, which reduces the sensitivity of plasma-based tests and, in our view, has likely contributed to the limited utility of plasma-based markers until more recent times.

It has been reported that up to 85% of dementia patients are seen by nonspecialists. Plasma-based biomarkers are likely to be particularly useful for this segment, though specialists could also find utility for these noninvasive tests. In their current state, plasma-based tests are primarily used as a screening tool and adjunct to clinical evaluation. In May 2025, the FDA approved the first blood-based test (Fujirebio's Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio) as a part of a diagnostic protocol for Alzheimer's disease. The agency conveyed enthusiasm toward blood-based tests over PET scans, describing PET scans as "a costly and time-consuming option and expose patients to radiation." Therefore, it is our view that serum-based assessments will play an increasing role in Alzheimer's disease diagnosis; we believe that the long-term dynamic regarding the relative clinical utility (versus PET tracers) remains difficult to project, though we expect to see a continued decrease in the use of CSF tests given their invasive nature.

It is important to highlight that it is likely not a winner-take-all scenario. Fluid biomarkers work in tandem with PET-based biomarkers given that the two methods measure different states of proteins that are associated with different stages of Alzheimer's disease. Therefore, there is consensus in the field that the diagnosis and evaluation of Alzheimer's disease is best informed through a combination approach that includes clinical presentation, visual reads, and/or biomarkers evaluation. For example, upon performing a plasma-based test, there are three possible outcomes: low, intermediate, or high biomarkers being present (associated with low, moderate, and high suspicion of Alzheimer's disease, respectively). In the low case, immediate intervention is likely unnecessary, and patients can be referred for clinical follow-up. In the intermediate case, PET or CSF should likely be carried out to confirm or deny the presence of Alzheimer's disease pathology. If the biomarker reading is classified as high, this can be enough to initiate anti-amyloid therapy. In this last case, while an amyloid-beta PET scan is typically deemed unnecessary from a diagnostic perspective, a follow-up PET scan is usually still obtained to establish a baseline and allow for monitoring disease progression and/or response to therapy. CSF and plasma-based tests are generally considered ineffective for this use since they reflect dynamic processes rather than the current state of plaque deposition. Therefore, it is difficult for these tests to assess the extent of pathology. Identifying patterns of deposition, which can provide insight into various pathologies, is also challenging with CSF and plasma-based tests and is typically best assessed with tau PET.

Despite the potential for plasma-based biomarkers to become an integral part of the Alzheimer's disease diagnostic landscape, plasma-based biomarkers are less well validated (especially in the real-world setting) than PET and CSF. Plasma-based biomarkers are also susceptible to co-pathologies, such as chronic kidney disease, which can mislead diagnosis. For example, as kidney function changes over time, plasma biomarker levels can be impacted, raising the risk of incidental findings that could appear related to changes in brain pathology. Furthermore, plasma p-tau levels are not pathology selective; in early stages of the disease, the biomarker reflects amyloid pathology, while tau pathology is reflected in later stages. As a result, confirmation of pathology may require analysis of both amyloid-beta and tau.

While not a comprehensive list, we compared PET-, CSF-, and plasma-based diagnostic tools across a variety of different parameters in exhibit 6. Overall, plasma-based tests appear to exhibit clear advantages from cost, access, and patient burden perspectives, but the insights that can be derived through visual assessment of the disease pathology are hard to overlook. Therefore, in our view, it is difficult to envision a scenario in which PET becomes entirely replaced by other diagnostic methods.

Exhibit 6
Radiopharmaceuticals
Comparison of Diagnostic Tools for Alzheimer's Disease

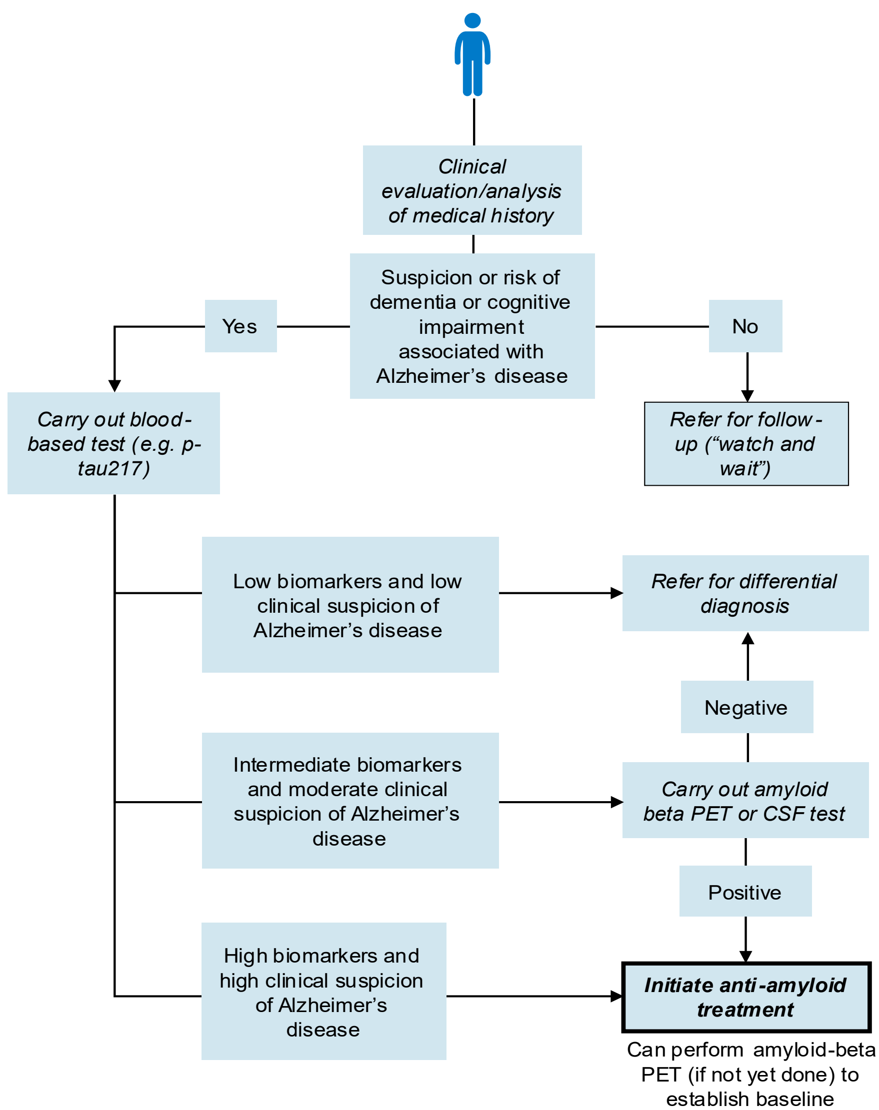
	PET	CSF	Plasma
Cost	High	Relatively low	Lowest
Access	Low in some areas	Relatively high	Highest
Patient burden	Low but can be time intensive	High	Low
Validation of performance	Fair	Fair	Limited
Inconclusive findings	Rare	Reported	Reported
Use as screening tool	Challenging	Challenging	Easy
Disease state measured	Current level of aggregation	Before aggregation	Before aggregation
Stage of disease that can be measured	Later	Early	Early
Ability to stage patients	Possible	Difficult	Difficult
Extent and distribution of pathology	Quantitative information	Not available	Not available
Ability to distinguish pathologies	Yes	No	No
Pathology measurement	Direct	Indirect	Indirect
Monitoring disease progression/response to therapy	Possible	Difficult	Difficult

Desirable characteristic
Less desirable characteristic
In between or undifferentiating
Sources: 2025 SNMMI annual meeting

We emphasize that blood-based tests are not typically covered by insurance (some tests are eligible for partial coverage), though the recently approved blood-based test has potential to be covered in the near to midterm. In addition, blood-based tests do not qualify a patient for anti-amyloid therapy and cannot be used as a replacement for PET imaging or CSF tests; however, KOLs are optimistic that this could change in the future. On the Centers for Medicare & Medicaid Services (CMS) website, there is now an option to select an "other" option (instead of just CSF test or PET scan) as the reason for initiating treatment.

In July 2025, the Alzheimer's Association released clinical practice guidelines for blood-based tests and specified that if sensitivity and specificity are above 90%, the blood-based test can be used as a substitute for PET or CSF. The potential workflow for how blood-based tests could be incorporated into diagnostic decision-making is provided in exhibit 7.

Exhibit 7
Radiopharmaceuticals
Potential Future Diagnostic Workflow for Alzheimer's Disease That Incorporates Blood-Based Tests



CSF=Cerebrospinal fluid. PET=Positron Emission Tomography.
Sources: SNMMI 2025 annual meeting and William Blair Equity Research

One of the current use-cases for blood-based tests is to identify patients who should likely not receive anti-amyloid therapy, thereby serving as a “rule out” metric when screening. In fact, in October 2025, the FDA cleared Roche’s Elecsys pTau181 blood test as a rule-out test in patients aged 55 years or older who are showing signs of cognitive decline. Patients with negative results avoid potentially invasive tests, while those with positive results are referred to additional testing. By potentially ruling out Alzheimer’s disease pathology, the test can also provide insight into other causes contributing to cognitive decline. Elecsys is also approved as a diagnostic confirmatory assay for amyloid pathology when combined with Elecsys β-Amyloid (1-42) CSF II, which measures levels of amyloid-beta 42. In addition, Roche is developing Elecsys Phospho-Tau (217P), which measures p-tau217, as a potential “rule in” assay across both the screening and diagnosis stages.

Theoretically, the ability to rule out patients through blood-based tests could reduce the need for PET imaging up front and overall reduce the use-case for PET scans in the subset of patients with low blood biomarkers. However, because amyloid PET remains the mainstay for helping physicians assess target engagement and treatment response to anti-amyloid beta treatment (CSF analysis or blood-based tests cannot effectively achieve these goals), KOLs envision that the volume of amyloid PET scans will continue to increase. In fact, blood-based testing appears to be replacing CSF analysis while more minimally impacting PET imaging. Overall, over the past six to seven months (since the first FDA approval of a blood-based test), PET scan volumes have not been noticeably affected.

Overview of the Alzheimer’s Disease Imaging Market

According to Maximize Market Research, the global Alzheimer’s disease diagnostic market was about $3.5 billion in 2023 and is expected to grow at a 12.8% compound annual rate to reach roughly $8 billion by 2030. Regarding PET imaging for Alzheimer’s disease, Lantheus projects that the U.S. market could grow to $1.5 billion by 2030 and to $2.5 billion by the mid-2030s. Specifically, the estimated 430,000 scans in 2030 are expected to consist of scans from staging (70%), screening (19%), and monitoring (12%). The list price for approved amyloid-beta PET agents ranges, based on CMS proposed reimbursement rates for 2026, from about $1,600 for Neuraceq to roughly $3,700 for Tauvid (exhibit 8).

Exhibit 8
Radiopharmaceuticals
Reimbursement Rates for PET-Based Alzheimer's Disease Imaging Agents

Product	Dose	Last TPT Rate (per dose)	2025 Rate (per dose)	2026 Proposed Rate (per dose)	Change % (2025 to 2026)	TPT Status
Amyvid	10 mCi	NA*	$2,194.62	**$1,881.87**	-14.3%	Expired
Neuraceq	8.1 mCi	NA*	$1,273.76	**$1,577.13**	23.8%	Expired
Vizamyl	5 mCi	NA*	$874.40	**$1,962.95**	124.5%	Expired
Tauvid	10 mCi	$3,710.00	$3,710.00	**$3,710.00**	0.0%	Active

*Time frame was prior to unbundling of high-cost diagnostic radiopharmaceuticals; therefore, there was no separate payment rate.

Sources: CMS addendum B files, FDA labels

As it stands today, we believe that the commercial success of amyloid-beta PET scans is highly dependent on the prerequisite of establishing amyloid-beta pathology prior to initiating treatment. Similarly, it is our view that the success of tau PET is highly dependent on the use of PET imaging to monitor disease progression and/or response to therapy and, perhaps even more important, to select patients for tau-targeted therapies, pending positive clinical and commercial developments. Therefore, we recognize that as the treatment landscape for Alzheimer’s disease and the availability of diagnostic agents evolves, the utility and use-case for amyloid-beta and tau PET agents will likely evolve accordingly. We also recognize that beyond the currently approved treatments for Alzheimer's disease, clinical testing of additional therapies that target amyloid-beta or tau are underway and could expand the need for diagnostics targeting these pathologies.

Beyond PET tracers targeting amyloid-beta and tau, there are several additional agents in development that target a-synuclein and TAR DNA-binding protein 43, which are associated with neurodegeneration. In addition, there are efforts aimed at developing agents for imaging neuroinflammation and synaptic density. Pending clinical trial and regulatory success, these agents could further bolster the Alzheimer's disease imaging market.

The future impact of blood-based tests on the volume of PET scans is currently difficult to assess. However, at least in the near term, we believe that amyloid PET will remain an invaluable component of the Alzheimer's disease diagnostic and treatment landscape. During its second quarter 2025 earnings call, Biogen noted a 5-times increase in monthly PET volume (primarily from Amyvid), which we believe bodes well for the PET imaging market as a whole. The company also noted that testing for blood-based biomarkers had roughly tripled over the past year, and during the third quarter 2025 earnings call, it was noted that more than 350,000 of these tests were expected to be carried out during 2025. Blood-based tests were also said to aid physicians in more quickly providing a definitive diagnosis. However, despite the increase in blood-based testing volume and the positive outlook, a 75% annual increase in PET scans was also noted (60,000 PET scans carried out year-to-date).

Amyloid-Beta PET Agents

Approved Amyloid-Beta PET Agents

Three PET agents are approved for measuring the density of amyloid-beta plaques in patients with cognitive impairment who are suspected of having Alzheimer's disease or another condition that may be contributing to cognitive decline. The approval of the three agents was based on studies that compared visual interpretation of pre-mortem PET scans to autopsy studies in populations nearing the end of life (enrollment criteria typically included life expectancy of less than one year).

Pathology assessment using PET is based on visually identifying the location of tracer uptake and retention. Typically, negative scans are limited to retention in white matter, while retention in the neocortex (predominantly grey matter) can indicate moderate to high amyloid-beta plaque density, which could be associated with Alzheimer's disease pathology. It is important to note that negative scans do not necessarily mean a complete absence of amyloid-beta plaques, and positive scans do not necessarily equate to intermediate-high Alzheimer's disease neuropathological change (ADNC, a measure of pathological changes associated with Alzheimer's disease, specifically related to amyloid-beta plaque deposition and NFT accumulation). While positive PET scans (indicating that moderate to frequent plaques are present) are often associated with Alzheimer's disease, they can also be indicative of other neurologic conditions or even normal cognition in the elderly population.

Although other types of brain imaging techniques are available, targeted PET exhibits distinct advantages. For example, compared to FDG-PET, amyloid-beta PET appears to have higher sensitivity in identifying pathology related to Alzheimer's disease. While amyloid-beta PET scans can be indicative of the presence or absence of neurologic dysfunction, the labels for all three agents specify that the scans alone are not sufficient for the basis of diagnosis and should be combined with other assessments.

To provide quantification of uptake, the standardized uptake value ratio (SUVR) is used and is defined as the steady-state ratio of uptake in a target region relative to uptake in a reference region that is minimally impacted by the disease. Another quantification tool that is gaining increased utility (and may be preferred over SUV_{max} or SUV_{mean}) is the centiloid (CL) scale, which is a linear transformation of SUVR that ranges from 0 to 100 CL units and provides a semiquantitative evaluation of amyloid-beta deposition based on a reference standard (^{11}C-PiB). In the scale, 0 represents an individual with no amyloid-beta deposition, and 100 designates a patient with mild to moderate Alzheimer's disease, though values outside the 0-to-100 range are possible. Although the thresholds of the scale are variable in range, below 10 CLs is typically associated with a negative read, while above 30 CL is generally classified as positive; more sensitive agents that could detect earlier-stage pathology are associated with lower thresholds. In the intermediate range of roughly 10 CL to 30 CL, it is more difficult to classify patients, and other methods of evaluation (clinical, visual reads, etc.) are likely to be more closely analyzed and could require a consensus assessment. In patients who begin accumulating amyloid-beta plaques, the rate of increase on the CL scale is roughly 3 CL to 5 CL per year.

Quantification of uptake was not a metric assessed in approval of the currently available amyloid-beta PET agents; in fact, quantification is used only as an adjunct for visual reads (though the agreement between quantification and visual reads of amyloid-beta PET are estimated to be 86% to 92%). In 2024, CL quantification software was cleared by the FDA for clinical use. One of the potential use-cases for the CL scale is as a tool for evaluating changes in amyloid plaque density over time, which would be particularly relevant when using PET tracers to monitor response to treatment. One of the unique advantages of the CL scale is that it allows comparison between various tracers, which is useful when baseline and follow-up scans are obtained with different PET agents. Measurements of SUVR cannot be compared unless obtained with the same tracer.

Historically, reimbursement of amyloid-beta PET scans imposed a headwind as the CMS reimbursed only up to one scan per lifetime and would reimburse only Medicare beneficiaries who were participating in certain clinical studies (referred to as coverage with evidence development). But in October 2023, CMS broadened coverage of amyloid-beta PET scans given the approval of amyloid-beta-targeted therapies and the recognition that these PET scans would be beneficial in selecting patients and monitoring their response to treatment. Following this change, the use of amyloid-beta PET agents expanded exponentially as they moved beyond predominantly clinical trial use and into the clinical setting. Correspondingly, there was a notable decrease in CSF tests.

Another important advancement was CMS's decision in 2024 to allow high-cost diagnostic radiopharmaceuticals to be unbundled and receive transitional pass-through (TPT) payment on a permanent basis. According to the agency, these changes were implemented to address the outsized cost contribution from novel diagnostic radiopharmaceuticals, thereby maintaining patient access to these higher-cost yet medically necessary imaging agents. However, one nuance is that since TPT status has expired for these agents, physicians must scan at stand-alone PET centers rather than at hospitals to achieve full reimbursement for Medicare patients. Otherwise, reimbursement for these patients occurs on a bundled basis. Despite these advancements, some KOLs in the field have reported difficulties in securing insurance coverage of repeat scans, for example to demonstrate clearance of amyloid after treatment with anti-amyloid therapy.

The Alzheimer's Association Workgroup and Society and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) provide guidelines on the recommended use-cases of PET imaging in the context of Alzheimer's disease. Based on updated guidelines published in early 2025, the agencies identified seven scenarios designated as "appropriate" for using amyloid-beta and tau PET. Broadly speaking, these scenarios for amyloid-beta PET include diagnosis and prognosis of patients with suspected or probable Alzheimer's disease pathology, to determine treatment eligibility, and to monitor patient response to therapy, with the latter two cases referring specifically to therapies targeting amyloid. The agency identified moderate to high confidence in amyloid-beta PET being appropriate for each of these situations.

Below, we discuss the three commercially available amyloid-beta PET imaging agents, all approved over a decade ago. A summary of the clinical trial results that led to approval of these diagnostics is provided in exhibit 9. Although the results vary based on the type of reader training (in-person versus electronic media), mean sensitivity ranges from 82% to 98% across the three agents, while mean specificity ranges from 77% to 95%. Neuraceq overall exhibited the highest sensitivity in the reported data but also the lowest specificity. Read accuracy appears comparable across all agents when considering "correct" readings (though it appears that Vizamyl may be the lowest numerically). Amyvid appears most prone to false negatives while least prone to false positives.

Exhibit 9
Radiopharmaceuticals
Approved PET Agents That Target Amyloid-Beta for Imaging Alzheimer's Disease

	Amyvid	Vizamyl	Neuraceq
Approval Year	2012	2013	2014
Drug Sponsor	Eli Lilly	GE Healthcare	Lantheus[1]
Administration Dose	370 MBq	185 MBq (followed by sodium chloride injection)	300 MBq
Image Acquisition Timing	10-minute scan after 30-50 minutes	20-minute scan after 90 minutes	15-20 minute scan after 45-130 minutes
Patients with Autopsy-Based Truth Standard[2]	59 patients	68 patients	82 patients
Baseline Characteristics[3]	Median age: 83 years Female: 50% Cognitive state: AD / dementing disorder / no CI / mild CI = 49% / 22% / 20% / 8%	Mean age: 81 years Female: 51% Cognitive state: AD / dementing disorder / no CI = 44% / 25% / 31%	Median age: 79 years Female: 48% Cognitive state: AD / dementing disorder / no CI = 67% / 18% / 16%
CERAD Classification at Autopsy (frequent/moderate/sparse/none)	30 / 9 / 5 / 15 patients	19 / 22 / 14 / 12 patients	31 / 21 /17 / 13 patients
Sensitivity Based on Majority Read[4]	92%	86%	98%
Specificity Based on Majority Read[4]	100%	92%	89%
Mean Sensitivity[5]			
In-person training	92% (69% - 95%)	88% (81% - 93%)	98% (96% - 98%)
Electronic media training	82% (69% - 92%)	93% (86% - 93%)	96% (90% - 100%)
Mean Specificity[5]			
In-person training	95% (90% - 100%)	88% (44% - 92%)	80% (77% - 83%)
Electronic media training	95% (90% - 95%)	84% (60% - 92%)	77% (47% - 80%)
Read Accuracy[5]			
Correct			
In-person training	90% (76% - 95%)	85% (75% - 90%)	91% (90% - 91%)
Electronic media training	86% (78% - 92%)	87% (81% - 90%)	86% (79% - 89%)
False negative			
In-person training	8% (3% - 20%)	7% (4% - 12%)	2% (1% - 2%)
Electronic media training	12% (5% - 20%)	6% (4% - 9%)	3% (0% - 6%)
False positive			
In-person training	2% (0% - 3%)	8% (3% - 21%)	7% (6% - 9%)
Electronic media training	2% (2% - 3%)	8% (3% - 15%)	12% (7% - 20%)
Fleiss's Kappa Statistic (in subjects with a truth standard)	0.75 (59 patients)	0.74 (104 patients)	0.75 (60 patients)
Common Adverse Events	Fatigue (1%) Musculoskeletal pain (1%) Nausea (1%) Headache (2%)	Dizziness (1%) Headache (1%) Nausea (1%) Flushing (2%) Increased blood pressure (2%)	Injection site reactions: Irritation (1%) Erythema (2%) Pain (4%)

[1]Neuraceq was developed by Piramal Imaging, which was renamed to Life Molecular Imaging (LMI) in 2018. LMI was then acquired by Lantheus in 2025.
[2]The truth standard is based on postmortem amyloid neuritic plaque density using CERAD classifications.
[3]Baseline characteristics for Neuraceq are from a 205-patient cohort.
[4]Majority read for Neuraceq is based on analysis from three independent readers in 74 patients.
[5]Based on averages across 5 readers (except for readers trained in-person for Neuraceq, which was 3 readers). The range is provided in parentheses.
AD=Alzheimer's disease. CERAD=Consortium to Establish a Registry for Alzheimer's Disease. CI=Cognitive impairment.
Sources: Curtis, C. et al. *Jama Neurology* (2015), Sabri, O. et al. *Alzheimer's & Dementia* (2015), and FDA labels

Each tracer is distinct in terms of which regions are evaluated when interpreting an image (and, correspondingly, which regions to exclude due to known off-target uptake). In addition, the amount of tracer uptake that is required to classify a region as positive or negative also varies among the agents. Overall, however, physicians in the field tend to view the agents as largely comparable, and preference is driven predominantly by availability from radiopharmacies and established contracts. Exhibit 10 provides an overview of some key parameters for visually interpreting scans obtained from the different agents.

Exhibit 10
Radiopharmaceuticals
Comparison of Visual Read Parameters for Approved Amyloid-Beta PET Agents

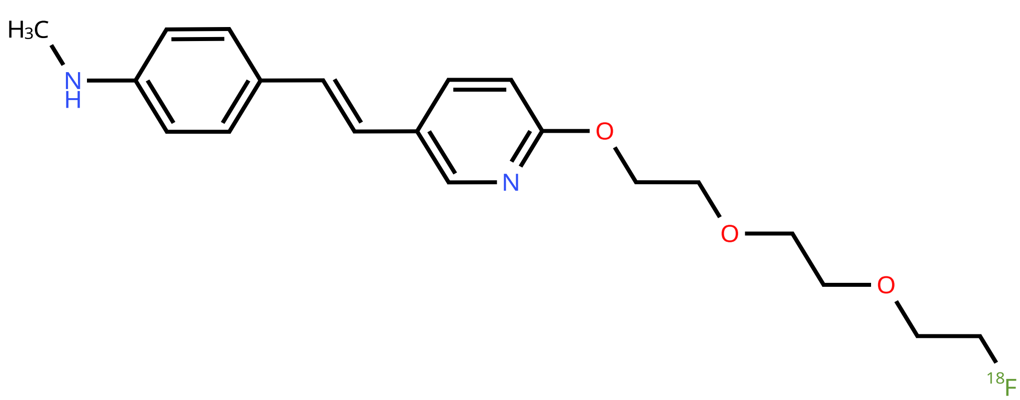
	Amyvid	**Vizamyl**	**Neuraceq**
Visualization scale	Gray	Color	Gray
Target regions for visual interpretation	Cortex (includes ***occipital lobe***)	Lateral temporal Inferolateral parietal Posterior cingulate/ precuneus Frontal ***Striatum***	Temporal Parietal Posterior cingulate/ precuneus Frontal
Regions excluded (due to nonspecific binding)	Striatum	Occipital lobe	Striatum Occipital lobe

Sources: 2025 SNMMI annual meeting

Amyvid

Amyvid was approved in 2012 and is marketed by Eli Lilly. The agent was originally developed by Avid Pharmaceuticals, which was acquired by Lilly in 2010. Amyvid incorporates fluorine-18 and a small molecule that binds to amyloid-beta aggregates (exhibit 11). Ten-minute image acquisition is carried out 30 to 50 minutes after administration of 370 MBq of Amyvid. Side effects are generally minimal, but headaches, musculoskeletal pain, fatigue, and nausea each occur in 1% to 2% of patients. Nonspecific binding in the striatum has been observed, so this region is excluded from visual assessment of PET scans when using Amyvid. The primary region analyzed is the cortex, which includes the occipital lobe. Notably, the occipital lobe is not assessed with Vizamyl or Neuraceq given that nonspecific binding has been reported for these tracers in that region.

Exhibit 11
Radiopharmaceuticals
Structure of Amyvid



Source: Created with MolDraw by William Blair Equity Research

Approval was based on three Phase III studies. The original study enrolled 226 patients with a life expectancy of 6 months or less or who were enrolled in an aging study with autopsy included in the protocol. Twenty-nine patients were included in the primary analysis. The median age was 85 years, roughly half were female, and 62% had dementia. The postmortem cortical amyloid burden correlated with median Amyvid scores with a correlation coefficient of 0.78 ($p<0.0001$).

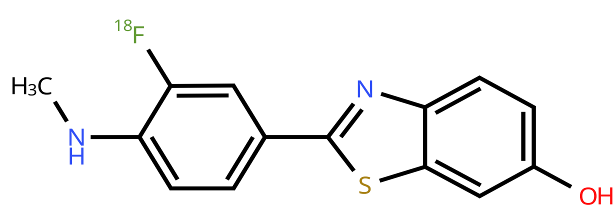
An extension study was then carried out to measure the sensitivity and specificity of Amyvid compared to a neuropathology assessment at autopsy in 59 patients, 35 of whom were also enrolled in the original study. The primary endpoints were sensitivity, specificity, and correlation based on Amyvid scan interpretation (based on the majority read from five independent readers) compared to amyloid plaque density at autopsy. This analysis was based on the Consortium to Establish a Registry for Alzheimer's Disease, or CERAD, system. Briefly, a negative image was defined by a CERAD classification of none (no neuritic plaque counts) or sparse (1 to 5 neuritic plaques), while a positive image was correlated with a classification of moderate (6 to 19 plaques) or frequent (20 or more plaques). This same system was also used in the Vizamyl and Neuraceq clinical trials. The autopsy must have been carried out within two years of Amyvid PET imaging, though sensitivity and specificity in patients with autopsy within one year of imaging were secondary endpoints.

In patients with a standard of truth based on autopsy, Amyvid demonstrated mean sensitivity of 92% and mean specificity of 95% across five readers who were trained in-person. Among five readers who were trained with electronic media, mean sensitivity and specificity were 82% and 95%, respectively. The metrics were 92% and 100% based on majority read. Additional details on the results, as well as patient baseline characteristics, are provided in the summary table (exhibit 9, on page 16).

Vizamyl

Vizamyl was approved in 2013 and is marketed by GE Healthcare. The agent incorporates fluorine-18 and a small-molecule binder (exhibit 12). Twenty-minute image acquisition is carried out 90 minutes after administration of 185 MBq of Vizamyl, followed by a sodium chloride solution flush. Unlike Amyvid and Neuraceq, which are visualized in gray scale, Vizamyl reports plaque density in color scale. In addition, the striatum is included as a target region for visual interpretation. For Amyvid and Neuraceq, this region is excluded due to known nonspecific binding.

Exhibit 12
Radiopharmaceuticals
Structure of Vizamyl



Source: Created with MolDraw by William Blair Equity Research

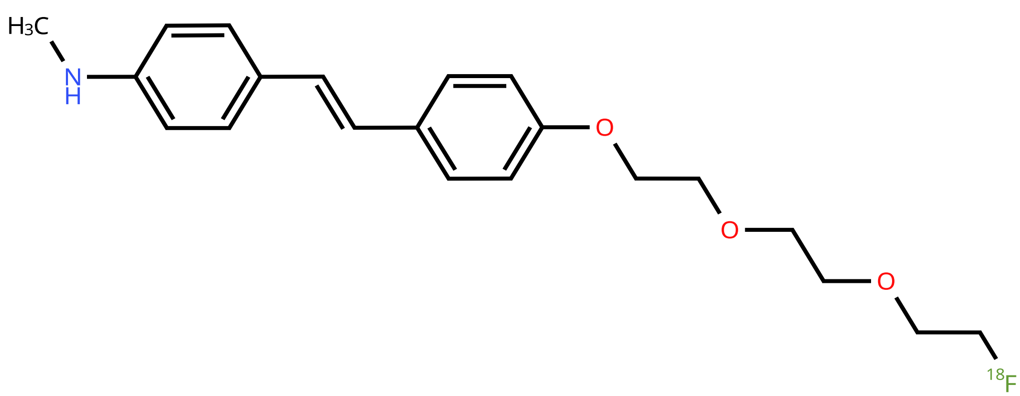
Vizamyl's approval was based on two clinical studies. In the first study, 68 patients (of 176 patients in the full analysis dataset) who passed away during the course of the study and had an autopsy were included in the primary analysis. The second study evaluated inter-reader reproducibility of images from individuals who participated in earlier studies. In both studies, scans were read by five independent readers. The first study used in-person training, while the second study relied on electronic media training. The CERAD classification (described in more detail above in the Amyvid section) was used as the truth standard.

When incorporating an autopsy-based standard of truth, the median sensitivity for Vizamyl in study one was 88% and in study two was 93%, while the median specificity in the two studies was 88% and 84%, respectively. In the second study, inter-reader reproducibility was characterized by a Fleiss's kappa score (which measures the degree of reliability between readers) of 0.83 when considering all 276 subjects and was 0.74 in the 104 individuals with a truth standard. Additional details on the results, as well as patient baseline characteristics, are provided in the summary table (exhibit 9, on page 16).

Neuraceq

Neuraceq, approved in 2014, was originally developed by Piramal Imaging, which was renamed to Life Molecular Imaging (LMI) in 2018. LMI was then acquired by Lantheus in 2025. The structure of Neuraceq is nearly identical to that of Amyvid and differs by only one atom (carbon instead of nitrogen, exhibit 13). Neuraceq is administered at 300 MBq, and a 15- to 20-minute scan is obtained 45 to 130 minutes after injection. The wide uptake window could provide flexibility from workflow and throughput perspectives. Both the striatum and occipital lobe are excluded from visual read analysis due to nonspecific binding.

Exhibit 13
Radiopharmaceuticals
Structure of Neuraceq



Source: Created with MolDraw by William Blair Equity Research

Neuraceq's approval was based on three clinical trials. The truth standard was again based on CERAD classifications (described in more detail above in the Amyvid section). The first study evaluated 205 individuals, though only 82 were autopsied and included in the analysis. The scans were analyzed by three independent readers who had been trained in-person. The second study evaluated images from the same 82 patients, but analysis was carried out by five independent readers trained through electronic media. The third study assessed reliability and reproducibility of image interpretation from the second study.

Median sensitivity from the first study was 98% and was 96% for the second study. Median specificity for study one and two was 80% and 77%, respectively. Image reproducibility in study two was defined by a Fleiss's kappa coefficient of 0.75 when considering 60 subjects with standard of truth. Additional details on the results, as well as patient baseline characteristics, are provided in the summary table (exhibit 9, on page 16).

Investigational Amyloid-Beta PET Agents

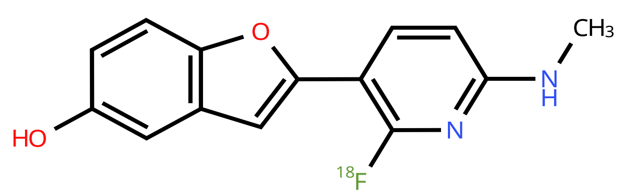
Broadly speaking, few amyloid-beta PET imaging agents are in development, possibly because three approved options already exist. Therefore, most innovation in the amyloid-beta diagnostic realm focuses on blood- or plasma-based detection. These types of agents are available already available from Quest Diagnostics, ALZpath, Roche, LabCorp, and C2N Diagnostics, and direct-to-consumer options have been available since 2023. Next-generation versions of blood-based testing aim to allow earlier detection of Alzheimer's disease and typically focus on the Aβ42 to Aβ40 ratio (e.g., the AD-Detect test from Quest). While Aβ40 levels tend to be consistent between people with and without plaque deposits, Aβ42 levels can be lowered by 40%-60% in patients with amyloid plaques. Therefore, a low ratio, typically around 0.15, suggests higher risk, while a high ratio indicates lower risk. Some tests, such as the PrecivityAD2 from C2N Diagnostics, also measure levels of p-tau217, which can be used as a surrogate biomarker for identifying Alzheimer's disease pathology. The estimated accuracy of PrecivityAD2, based on clinical studies, is 88% to 92%.

There is some speculation that given the trajectory of improvement in blood-based test performance, these tests could eventually replace or considerably reduce CSF analysis and brain scans, with some believing that next-generation blood tests exhibit superior performance compared to the more traditional approaches. Potential use-cases under evaluation for blood-based tests include screening and early diagnosis. However, while these tests are available, most are not fully approved by the FDA and thus are not typically covered by insurance. In addition, as discussed earlier in the report, PET imaging appears to be an integral component of the Alzheimer's disease diagnostic landscape, and this is unlikely to change in the near term. Therefore, we believe that the most probable use-case for plasma-based tests, when considering the current landscape, is as a prescreening tool to identify patients who should receive further testing with CSF or PET (i.e., those in the "intermediate" range).

NAV-4694

NAV-4694 (exhibit 14) is a Phase III agent that was acquired by Lantheus in 2024 when the company bought Meilleur Technologies. There are currently several Phase II studies and one Phase III study of NAV-4694 as a diagnostic for Alzheimer's disease listed on the clinicaltrials.gov site, but the statuses are designated as unknown (the Phase III trial lists an estimated completion data of September 2018). Lantheus aims to submit an NDA to the FDA in 2026.

Exhibit 14
Radiopharmaceuticals
Structure of NAV-4694



Source: Created with MolDraw by William Blair Equity Research

Lantheus believes that NAV-4694 could allow earlier detection of Alzheimer's disease, thereby enabling faster initiation of therapeutic interventions. It is hypothesized that NAV-4694's earlier detection is driven by lower nonspecific binding to white matter, a greater dynamic range, and improvements in signal-to-noise compared to the approved agents discussed above. Reduction in off-target binding could also facilitate easier scan readings in the clinical setting due to greater contrast between grey matter and white matter. The SUVR threshold for determining amyloid-beta positivity using NAV-4694 has been estimated to be 1.55.

Based on a study employing the centiloid scale, NAV-4694 aligned closely with the reference agent (^{11}C-PiB, a common reference standard) and demonstrated numerically lower variance compared to Amyvid, Vizamyl, and Neuraceq (3.7 versus 12, 5.4, and 6.8, respectively) and a higher R^2 value (0.99 versus 0.89, 0.95, and 0.96). Another study published in 2023 demonstrated that NAV-4694 could detect longitudinal accumulation of amyloid-beta from baseline to two-year follow-up. Minimal changes in SUVR were observed in young adults and cognitively unimpaired individuals who were negative for amyloid-beta. However, there were notable changes in SUVR (regional increases in most cases, but also some directional regional decreases) in individuals who were cognitively impaired or unimpaired, each with positive amyloid-beta, or who had Alzheimer's disease.

Tau PET Agents

Approved Tau PET Agents

Mechanistically, tau PET agents target PHFs (recall that PHFs are the building blocks of NFTs). Within Alzheimer's disease pathology, NFTs are formed through the mixing of 3R and 4R isoform tangles, which leads to a different structure than other neurodegenerative diseases that are characterized by NFTs formed from only 3R or only 4R isoforms. Therefore, in many cases (including for Tauvid, discussed in more detail below), agents that bind to 3R/4R NFTs specifically cannot also bind to 3R NFTs or 4R NFTs.

As previously highlighted, monitoring NFTs can allow tracking of disease progression, although the presence of NFTs alone cannot diagnose Alzheimer's disease without also confirming the presence of amyloid-beta plaques. Therefore, the use-case for tau imaging could include identifying the stage of the disease, monitoring progression of the disease following diagnosis, and assessing response to therapy. In the future, it could also be used as a tool to select patients for tau-directed therapies, which, while not yet approved, are continuing to be investigated in the field. Compared to CSF tests, tau PET imaging is said to be more sensitive to changes over time and is particularly superior in later stages of the disease. According to the guidelines from the Alzheimer's Association Workgroup and SNMMI, the identified appropriate use-cases for tau PET generally align with those for amyloid PET, but some of the specific patient groups differ, and the use-case for monitoring response to therapy is designated as "uncertain." In general, compared to amyloid-beta PET, tau PET is recognized as having many more scenarios deemed as uncertain. Therefore, we view the use-cases for tau PET as continuing to evolve.

Another potential use-case for tau PET is identifying patients most likely to benefit from treatment. Abnormalities in tau PET often correlate with onset of neurodegeneration and clinical symptoms (in contrast, amyloid PET can become abnormal 20 to 30 years before clinical symptoms present). Therefore, in patients who are asymptomatic but have positive amyloid PET scans, tau PET can help predict when clinical symptoms will begin. This can be useful for stratifying patients into early or later stages of disease, and identifying patients with early-stage disease can lead to earlier treatment and more effective outcomes.

Interpretation of scans is based on visual assessment, with negative scans being characterized by absence of neocortical uptake or limited to only the medial temporal, anterolateral temporal, or frontal cortex regions. Similar to amyloid PET tracers, the approval of Tauvid was based on studies comparing visual interpretation of pre-mortem PET scans to autopsy studies in a population nearing the end of life. One of the limitations of Tauvid is that the agent exhibits limited sensitivity in earlier-stage settings when a lesser degree of tau pathology is present. Therefore, its use-case should potentially be restricted to more advanced cases of disease.

For amyloid-beta, the CL scale is used for quantification and comparing deposition both over time and between different tracers. However, no such scale exists for tau as there is no established reference standard (as previously discussed, the reference standard for amyloid-beta is ^{11}C-PiB). A universal scale for tau PET quantification remains in need of development, but some attempts have demonstrated potential, such as the CenTauR scale.

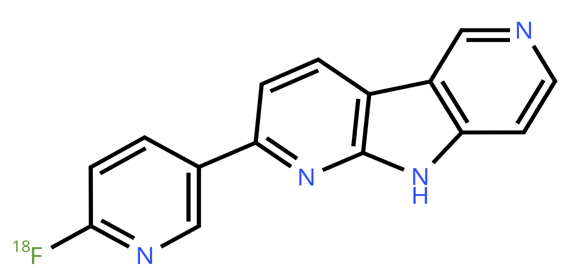
Despite the promise of tau PET, it is not routinely carried out at standard imaging centers. Furthermore, even when deemed appropriate for use, tau PET tracers can be difficult to access, though they appear on formularies and therefore can be reimbursed. According to the SNMMI workgroup and starting in January 2025, CMS covers tau PET based on discretion from local Medicare administrative contractors, which are regional private insurers that work with CMS to process medical claims. Some physicians in the field expect this dynamic to change in the near term as the use-cases for tau PET become more clearly defined and appreciated. Given that there is correlation between the diffusivity of tau in the brain and response to anti-amyloid treatment (more diffuse tau is associated with a lower likelihood of response and vice versa), a common reason for physicians to order tau PET is to assess the likelihood of a patient responding to treatment.

Similar to amyloid-beta, blood-based tests also exist for tau. Immunoassays for detecting p-tau217, p-tau181, and p-tau231 are available, though p-tau217 has been identified as a particularly promising biomarker and is said to be associated with both amyloid-beta and tau pathology. P-tau (phosphorylated tau), specifically p-tau181 and p-tau217, have a greater association with Alzheimer's disease compared to total tau levels, which can be elevated due to other conditions, such as stroke, traumatic brain injury, or Creutzfeldt-Jakob disease, and therefore are not specific to Alzheimer's disease pathology. Some studies suggest that in the early stages of the disease, plasma measurements of p-tau offer a more sensitive measurement of Alzheimer's disease pathology compared to tau PET (though still not as sensitive as amyloid-beta PET). Specifically, blood-based tests measure soluble forms of p-tau (and Aβ42) and therefore may detect disease at earlier time points compared to PET that binds protein inclusion aggregates. Therefore, plasma measurement could offer a convenient method for identifying patients who may be candidates for early therapeutic intervention.

Tauvid

In 2020, Eli Lilly received FDA approval for Tauvid, a fluorine-18-based PET imaging agent (exhibit 15) designed to measure the density and distribution of aggregated tau NFTs in adults with cognitive impairment. The agent is administered at 370 MBq and is imaged roughly 80 minutes after injection. Tauvid was the first (and currently only) radioactive diagnostic approved to image tau tangles as it addressed some of the limitations observed with first-generation tau imaging agents that did not obtain approval. These limitations included high nonspecific binding in white matter (^{18}F-THF523), light sensitivity (^{11}C-PBB3), and defluorination (^{18}F-T808), which was discovered through high uptake in bone.

Exhibit 15
Radiopharmaceuticals
Structure of Tauvid



Source: Created with MolDraw by William Blair Equity Research

Approval of Tauvid was based on two studies, each with five independent readers. The first study demonstrated sensitivity that ranged from 92% to 100% (median of 95%) and specificity ranging from 52% to 92% (median of 75%) in 64 terminally ill patients with either normal or impaired cognitive ability. These values are based on the B score system, though results based on ADNC were also reported (and generally correlated well with B score results). The second study evaluated the same patients as the first study with 18 additional terminally ill patients and 159 more patients who were being evaluated for Alzheimer's disease and who had been characterized by cognitive impairment. The Fleiss's kappa statistic in this study was 0.87 across all 241 patients, 0.82 in terminally ill patients, and 0.90 in the 159 indicated patients. The trial results are summarized in exhibit 16.

Exhibit 16
Radiopharmaceuticals
Phase III Trial Results of Tauvid PET Imaging in Alzheimer's Disease

Study ID	Study 1: NCT02516046 Study 2: NCT03901092	
Administration Dose	370 MBq	
Image Acquisition Timing	20-minute scan after 80 minutes	
Enrollment in Primary Cohort[1]	64 patients	
Baseline Characteristics	Cognitive state: Normal / mild impairment / dementia = 22% / 2% / 77% Median age: 82.5 years Female: 53% MMSE score: 18 (26 patients) IQCODE score: 4.5 (59 patients)	
Corresponding Metric for Scan Performance (a "positive" scan)[2]	*B3 NFT score*	*High ADNC*
Sensitivity	95% (92% - 100%)	96% (95% - 100%)
Specificity	75% (52% - 92%)	75% (50% - 92%)
Negative Predictive Value	91% (86% - 100%)	94% (91% - 100%)
Positive Predictive Value	86% (83% - 95%)	86% (75% - 95%)
Accuracy	87% (81% - 92%)	88% (80% - 94%)
Fleiss's Kappa Statistic[3]	0.87	

[1]Includes patients enrolled in study 1 who had an autopsy.
[2]Values for scan performance metrics are averages from five readers in study 1. The range is provided in parentheses.
[3]Value is based on five readers in study 2 (different readers than in study 1) who evaluated scans from 241 patients, including the 64 patients from the primary cohort in study 1.
ADNC=Alzheimer's disease neuropathologic change. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. MMSE=Mini-Mental State Examination. NFT=Neurofibrillary tangles
Sources: Fleisher, A. et al. *JAMA Neurology* (2020), FDA labels

While Tauvid is the only approved tau imaging agent, important limitations exist. Specifically, the agent is known to exhibit off-target binding in certain areas of the brain, which can lead to false positives. It can also be difficult to diagnose early stages of Alzheimer's disease with Tauvid. Many of the next-generation tau agents are specifically designed to exhibit reduced off-target binding compared to Tauvid and other first-generation agents (which includes ^{11}C-PBB3 and the ^{18}F-THK class of agents). Another limitation of Tauvid is that it only binds to the 3R/4R isoform of tau that is associated with Alzheimer's disease. Therefore, it cannot be used to detect diseases characterized by 3R tauopathies (e.g., Pick's disease) or 4R tauopathies, such as PSP and CBD.

Investigational Tau PET Agents

Compared to amyloid-beta PET agents, more candidates are in development for targeting tau, possibly because only a single agent is currently approved. These next-generation agents aim to address many of the limitations associated with Tauvid, namely, lower off-target binding and the potential to address tauopathies beyond Alzheimer's disease (for agents that target both 3R and 4R isomers). A summary of the fluorine-18-based agents in development for imaging tau is provided in exhibit 17, and we offer additional commentary below.

Exhibit 17
Radiopharmaceuticals
Fluorine-18-Based Tau-Targeted PET Agents Under Investigation for Imaging Alzheimer's Disease

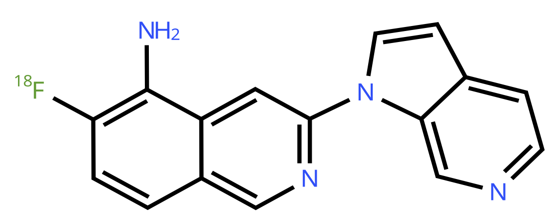
Agent	Sponsor	Phase of Development	Potential Advantages
MK-6240	Lantheus	Phase III	- Reduced off-target binding
PI-2620	Lantheus	Phase III	- May bind 3R and 4R - Reduced off-target binding
APN-1607	Aprinoia Therapeutics	Phase III (China) Phase II (U.S., Taiwan, Japan)	- May bind 3R and 4R
RO-948	Roche	Phase I[1]	- Reduced off-target binding - Faster kinetics
GTP1	Genentech	Phase I[2]	-

[1]The Phase I study is a comparison study that includes MK6240 and GTP1. A 120-patient study evaluating RO948 versus amyloid PET is recruiting, but the phase is not specified.
[2]The ongoing Phase I study is a comparison study that includes MK6240 and RO948. Other Phase I studies focused on GTP1 have been completed.
Sources: Company reports and clinicaltrials.gov

MK-6240

MK-6240 is a fluorine-18-based PET imaging agent (exhibit 18) for Alzheimer's disease that targets tau tangles. Lantheus gained access to the asset through the acquisition of Cerveau Technologies in early 2023. MK-6240 was developed by Merck, and global development and commercialization rights were granted to Cerveau in early 2017. MK-6240 has completed Phase III evaluation, and the NDA has been accepted by the FDA with a PDUFA date of August 13, 2026.

Exhibit 18
Radiopharmaceuticals
Structure of MK-6240



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According to Lantheus, MK-6240 has the potential to detect earlier stages of disease compared to other tau tracers. Furthermore, based on a study that compared MK-6240 to Tauvid, MK-6240 was more specific, exhibited markedly reduced off-target binding, and had a greater dynamic range (resulting from higher affinity for the tau target). However, we highlight that MK-6240 only targets the mixed 3R/4R isoform of tau and therefore cannot be used to image non-Alzheimer's disease pathologies.

Based on a clinical study in roughly 100 patients, MK-6240 was able to approximate Braak staging and provide a visual representation of a patient's progression with no off-target binding to gray matter. The imaging agent also demonstrated high sensitivity and was able to detect tau tangles at early stages. These results were corroborated by another study in 125 patients in which MK-6240 imaging allowed correlations to be drawn between the level of cognitive impairment and the degree of tau accumulation in different Braak regions. Tau accumulation was detected in both symptomatic and asymptomatic patients. In addition, postmortem studies supported MK-6240 as a useful tool for staging tau pathology. We also highlight that MK-6240 is being used to measure tau in the Phase III AHEAD 3-45 trial and the prior Phase III Clarity AD trial of Eisai and Biogen's Leqembi in Alzheimer's disease, which we believe is a demonstration of MK-6240's clinical potential.

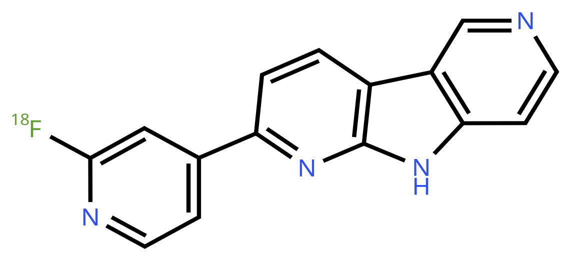
In an ongoing longitudinal study evaluating Tauvid, MK-6240, PI-2620, and RO948 (PI-2620 and RO948 are discussed later in the report) head-to-head, case studies suggested higher uptake of MK-6240 compared to the other agents, possibly due to a broader dynamic range. In another head-to-head study of the same agents, MK-6240 demonstrated the strongest overall association with the p-tau217 biomarker, suggesting that blood tests could be used as a tool for selecting patients who could benefit from a follow-up PET scan. MK-6240 was also described as more sensitive compared to both p-tau and Tauvid. An ongoing Phase I trial is evaluating MK-6240 compared to Tauvid and is aiming to elucidate the clinical use-cases of each agent.

Earlier this year, Lantheus announced that two pivotal studies of MK-6240 met the primary endpoints. The trials were designed to evaluate the agent's sensitivity and specificity. However, detailed data were not disclosed, so we believe it is difficult to contextualize the clinical performance of MK-6240 and to assess the potential read-through to market uptake.

PI-2620

PI-2620 was developed through a research collaboration between AC Immune and LMI, but Lantheus gained access to the asset through its acquisition of LMI in 2025. PI-2620 is currently in Phase III investigation for Alzheimer's disease, though the agent is also being investigated in PSP and CBD. In August 2024, PI-2620 received fast-track designation from the FDA for all three indications. The small-molecule binder is a derivative of Tauvid and incorporates fluorine-18 (exhibit 19). PI-2620 binds to 3R/4R tau isoforms, but data suggest that the agent may also bind to only-3R and only-4R isoforms. Therefore, the agent could have broader applicability for diagnosing neurodegenerative disorders beyond Alzheimer's disease. However, studies suggest that binding of PI-2620 to 4R tauopathies is less stable compared with binding to 3R/4R tauopathies.

Exhibit 19
Radiopharmaceuticals
Structure of PI-2620



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Based on a first-in-human study, PI-2620 demonstrated peak cerebral uptake at 5 minutes post-injection with SUVR plateauing at 40 minutes after administration. This could lead to a wide imaging window of 30 to 90 minutes after injection. In addition to high initial uptake, there was minimal off-target binding and rapid clearance of PI-2620 from regions of the brain lacking accumulation of tau.

In a Phase II one-year longitudinal study, PI-2620 was used to visualize tau deposition in both early-onset and late-onset patients with Alzheimer's disease. At baseline, global SUVRs were highest in early-onset patients (1.54, p<0.001; 17 patients) compared to late-onset patients (1.18; 20 patients) and those with negative amyloid-beta scans (1.04; 15 patients). At the one-year follow-up, the mean percent difference was 8.4% for early-onset patients, compared to 3.9% for late-onset patients and 0.3% for patients with negative amyloid-beta scans. Overall, changes in tau accumulation over time, based on PI-2620 PET images, correlated with change in patients' cognitive ability. These results suggested PI-2620's potential utility in selecting patients for treatment and monitoring subsequent response. A summary of the Phase II results is provided in exhibit 20.

Exhibit 20
Radiopharmaceuticals
Phase II Trial Results of 18F-PI-2620 PET in Individuals With Normal Cognitive Ability, Mild Cognitive Impairment, or Alzheimer's Disease

Trial ID	NCT03903211		
Administration Dose	259 MBq		
Image Acquisition Timing	After 60-90 minutes		
Enrollment	52 participants		
Alzheimer's Classification	Amyloid-beta-negative	Amyloid-beta-positive Late-onset (≥65 years)	Amyloid-beta-positive Early-onset (<65 years)
Number of Patients	15 (7 NC / 8 MCI)	20 (9 MCI / 11 AD)	17 (11 MCI / 6 AD)
Baseline Characteristics	Age: 64 years / 73 years Female: 71% / 50% Hypertension: 57% / 63% Diabetes: 0% / 0% Hyperlipidemia: 43% / 50% ApoE ε4 carrier: 57% / 13%	Age: 75 years / 78 years Onset age: 70 years / 73 years Female: 67% / 55% Hypertension: 44% / 73% Diabetes: 11% / 36% Hyperlipidemia: 44% / 27% ApoE ε4 carrier: 56% / 64%	Age: 62 years / 66 years Onset age: 58 years / 58 years Female: 73% / 83% Hypertension: 27% / 50% Diabetes: 18% / 0% Hyperlipidemia: 18% / 33% ApoE ε4 carrier: 73% / 67%
Global SUVR			
Baseline	1.04	1.18	1.54 (p<0.001)
Follow-up[1]	1.04	1.23	1.67
% difference	0.3%	3.9%	8.4%

[1]Roughly one-year after initial scan.
AD=Alzheimer's disease. MCI=Mild cognitive impairment. NC=Normal cognition. SUVR=Standardized uptake value ratio.
Sources: Oh, M. et al. *J Nucl Med* (2024)

There are currently two Phase III studies listed on clinicaltrials.gov. One is a histopathological study for detecting tau deposition in 200 patients with Alzheimer's disease or healthy controls, and the estimated primary completion date is December 2025 (exhibit 21). The primary endpoint is PI-2620's ability to classify patients at autopsy as tau positive or tau negative based on NFT score with negative being B0 or B1 and positive being B2 or B3. We highlight that the definition of a positive NFT appears to differ from the definition in the Phase III trial that led to approval of Tauvid, which specified B3 as positive and B0-B2 as negative. However, the overall designs are similar, and the primary and secondary endpoints of the Phase III study of PI-2620 were also key metrics for the Phase III trial of Tauvid. The analysis for the PI-2620 trial will be carried out by five independent readers, and the endpoint will be met if the lower bound of the 95% confidence intervals for sensitivity and specificity is 50% or higher for at least three of the five readers. The other Phase III trial is using PI-2620 to detect tau accumulation in patients with frontotemporal lobar degeneration or non-amnestic Alzheimer's disease with an estimated completion date of August 2028.

Exhibit 21
Radiopharmaceuticals
Phase III Trial Design of ^{18}F-PI-2620 PET in Individuals With Alzheimer's Disease

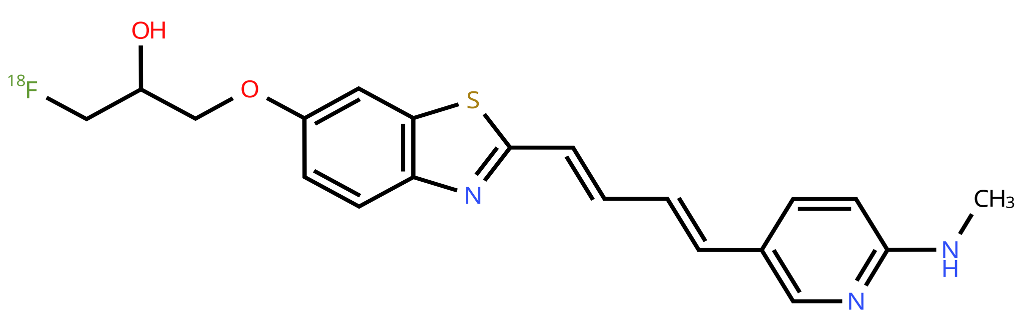
Trial ID	NCT05641688
Administration Dose	185 MBq
Target Enrollment	200 participants
Enrollment Criteria	50 years of age or older Projected life expectancy of ≤ 1 year
Primary Endpoint	**Diagnostic ability to identify NFT pathology associated with Alzheimer's disease (based on NFT score: B0 or B1 = negative and B2 or B3 = positive)[1]**
Secondary Endpoints	Diagnostic ability to identify levels of ADNC (based on NIA-AA criteria)[1] Inter-reader agreement
Timing	Primary completion: December 2025[2]

[1]Based on visual analysis from 5 independent readers and compared to standard of truth based on autopsy. The lower bound of the 95% confidence intervals for sensitivity and specificity must be at least 50% for 3 of the 5 readers in order for the endpoint to be met.
[2]Based on estimate from clinicaltrials.gov.
ADNC=Alzheimer's disease neuropathologic change. NFT=Neurofibrillary tangles.
Source: clinicaltrials.gov

APN-1607

APN-1607 (exhibit 22) is being developed by Aprinoia Therapeutics and is a pan-tau tracer that targets the 3R/4R isoform with additional evidence for targeting just 3R and just 4R tau isoforms. The compound is a derivative of PBB3, which was developed in 2014 as a carbon-11-based tracer. However, APN-1607 is said to exhibit broader accessibility and superior signal-to-noise compared to the parent molecule. Given the pan-tau nature, applications of APN-1607 could span beyond Alzheimer's disease, and studies have demonstrated APN-1607's ability to also identify aggregated tau in PSP, CBD, and Pick's disease.

Exhibit 22
Radiopharmaceuticals
Structure of APN-1607



Source: Created with MolDraw by William Blair Equity Research

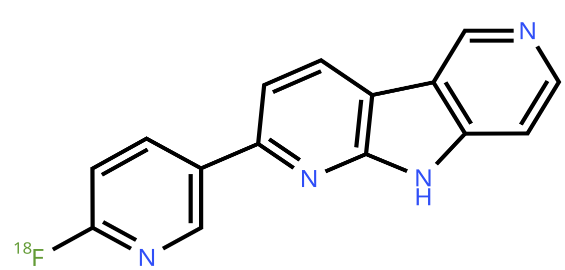
In a 46-patient study from 2023, APN-1607 was able to identify patients with: Alzheimer's disease who had dementia ($p<0.001$); Alzheimer's disease with mild cognitive impairment; or no cognitive impairment. These results were based on average visual scores from four readers. The consensus among the four readers was described as having an intraclass correlation coefficient of 0.880, which is associated with good to excellent agreement depending on the interpretation scoring system that is applied. The visual scores were also associated with SUVR ($p<0.0001$) and the Clinical Dementia Rating – sum of box score ($p<0.0001$), which is a scale ranging from 0 to 18 that determines stage of dementia. A Phase II trial is active with an estimated primary completion date, according to clinicaltrials.gov, of September 2024 (the last update was posted in mid-2023). In addition, a China-based Phase III trial of APN-1607 as a diagnostic for Alzheimer's disease completed enrollment in December 2023, and the trial was designed to support approval. However, based on clinicaltrials.gov, the status of the trial is unknown.

Outside Alzheimer's disease, APN-1607 received FDA orphan drug designation for diagnosing PSP in 2017 and received fast-track designation in mid-2024 for the same indication. A Phase III trial of APN-1607 as a diagnostic in PSP received a "study may proceed" letter from the FDA in December 2023, and the design has previously been outlined by Aprinoia. However, although the trial was planned for 2024, the status appears to be unknown. Based on company documents, the Phase III trial is slated to enroll 130 patients with possible, probable, or non-PSP. Five readers will evaluate the images, and sensitivity and specificity at 12 months compared to consensus from an expert panel are the coprimary endpoints. A Phase I study in 12 patients completed in early 2024, but the results have not been released to our knowledge.

RO948

RO948 was developed by Roche and appears to preferentially target 3R/4R isoform of tau, which likely limits the use-case to imaging patients with Alzheimer's disease pathology (evidence of binding to just 3R or just 4R isoforms is lacking). The agent (exhibit 23) is a derivative of Tauvid, but compared to Tauvid, RO948 is said to have faster kinetics and lower off-target binding, particularly in the basal ganglia regions. The agent is currently being investigated in a 38-patient Phase I trial that is evaluating RO948, along with MK-6240 and GTP1, in patients with Alzheimer's disease and in healthy controls. The study is designed to demonstrate a lack of off-target binding for the three agents, and the estimated completion date, according to clinicaltrials.gov, is June 2027. In addition, a 120-patient trial (phase not specified), with an estimated completion in August 2027, is investigating the value of tau-based PET imaging (using RO948) versus amyloid-beta-based PET imaging in diagnosing Alzheimer's disease.

Exhibit 23
Radiopharmaceuticals
Structure of RO-948



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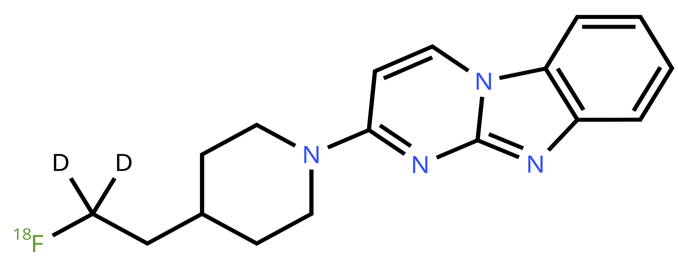
Based on a study in 613 individuals characterized as having no cognitive impairment, mild cognitive impairment, Alzheimer's disease dementia, or a non-Alzheimer's-disease disorder, RO948 exhibited highest retention in the Alzheimer's disease dementia patients and could distinguish these individuals from others in the study as RO948 did not bind significantly to patients with non-Alzheimer's-disease disorders. Furthermore, performance was generally superior to MRI and CSF measurements. For CSF specifically, amyloid-beta biomarkers, including the Aβ42 to Aβ40 ratio, were said to plateau in relatively early stages of the disease and therefore may have limited utility, while imaging approaches can be used for longitudinal evaluation. The study results also suggested that PET-based imaging of tau can help, along with amyloid-beta biomarker tests, to identify early-onset dementia and may be able to identify late-onset dementia without additional tests (e.g., cerebrospinal fluid analysis and/or amyloid-beta PET), given that positive RO948 PET scans almost perfectly correlated with cases of positive amyloid-beta. Similar to MK-6240 and PI-2620, off-target binding in the skull meninges has been reported but did not appear to impact the diagnostic performance of RO948 in this study.

GTP1

GTP1 (exhibit 24) was developed by Genentech, a subsidiary of Roche. In a comparison of GTP1 to PI-2620 and MK-6240 in 49 patients, all agents were taken up to a similar extent in patients with Alzheimer's disease, based on SUVR values, with the lowest correlation among agents being in patients with Braak II staging. For Braak II patients, MK-6240 appeared to bind with higher affinity, leading to a wider dynamic range and higher SUVR. Off-target uptake patterns also differed among the agents. GTP1 was taken up the most in subcortical structures (e.g., thalamus, caudate, putamen, and globus pallidus), and it was hypothesized that this would not interfere with quantification in patients with Alzheimer's disease. PI-2620 and MK-6240, on the other hand, were preferentially taken up in the skull meninges. In another study, greater SUVR values for GTP1 PET correlated with cognitive decline in patients with AD.

Exhibit 24
Radiopharmaceuticals
Structure of GTP1



Source: Created with MolDraw by William Blair Equity Research

The current development status of GTP1 in Alzheimer's disease is somewhat uncertain. The agent has completed several Phase I studies: one in the United States, completed in 2019; one in healthy Japanese individuals, completed in 2020; and one evaluating GTP1 versus PI-2620 or MK-6240, completed in 2023. In addition, GTP1 has been used in Phase II studies evaluating Roche's crenezumab (trial completed in 2022) and UCB's bepranemab (trial was completed in August 2024). The agent is currently being investigated in a 38-patient Phase I trial that is evaluating GTP1 along with MK-6240 and RO948 in patients with Alzheimer's disease and in healthy controls.

Outlook

Given that approved therapies for treating Alzheimer's disease require confirmation of amyloid-beta pathology, most often through imaging, we currently recognize a clear use-case for amyloid-beta PET agents. Similarly, it is our view that tau PET agents could find continued utility in monitoring disease progression and/or response to treatment, as well as to select patients for tau-targeted therapy, ***pending successful clinical and regulatory development of drug candidates.*** However, we also acknowledge the emergence of blood-based biomarker tests, which provide a convenient and cost-effective method for identifying patients who are clear candidates or noncandidates for anti-amyloid therapy or for whom a follow-up PET scan or CSF test is necessary. While the use-case of PET for diagnosing and monitoring Alzheimer's disease may be called into question as blood-based tests become increasingly available, it is our view that PET-based imaging provides critical structural information about the pathology that cannot be gleaned from plasma-based biomarkers (or CSF tests). Therefore, while plasma-based biomarkers will undoubtedly become a key component of the diagnostic landscape for managing Alzheimer's disease, we believe that PET will continue to play an integral role. For tau PET specifically, we believe that uptake hinges heavily on a number of factors, including regulatory approval of tau-directed therapies; development of a more widely accepted quantification method; and more clearly defined reimbursement procedures.

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Biogen Inc. (Outperform)	$182.61
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Eli Lilly and Company	$1,064.04
Johnson & Johnson	$204.79
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Roche Holding AG	$51.63
Sanofi	$48.17

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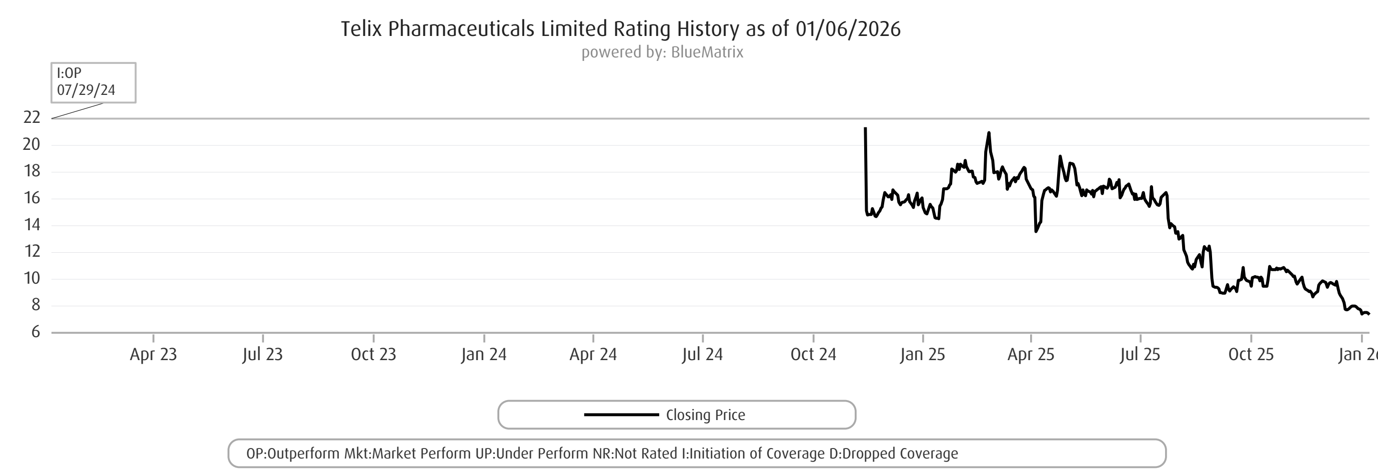
DOW JONES: 48996.10
S&P 500: 6920.93
NASDAQ: 23584.30

Source: FactSet & William Blair



Source: FactSet & William Blair

Additional information is available upon request.

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Outperform (Buy)	71	Outperform (Buy)	11
Market Perform (Hold)	28	Market Perform (Hold)	3
Underperform (Sell)	1	Underperform (Sell)	0

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