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Louis B. Jacques, MD
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Centers for Medicare and Medicaid Services
Mail Stop S3-02-01
7500 Security Boulevard
Baltimore, MD 21244-1850

RE: Request for Reconsideration of Medicare National Coverage Determinations Manual, § 220.6, Positron Emission Tomography (PET) Scans

Dear Dr. Jacques:

This is a formal request to reopen and revise Section 220.6 of the Medicare National Coverage Determinations Manual, which addresses coverage for Positron Emission Tomography (PET) scans. This letter and the accompanying appendices highlight the body of clinical evidence supporting the use of PET with a radiopharmaceutical to image beta-amyloid plaques in order to provide physicians with accurate and reliable diagnostic information with which to evaluate patients within the Medicare population suffering from cognitive impairment and being evaluated for Alzheimer's disease and other causes of cognitive decline.

Introduction of Beta-amyloid and Reconsideration Request

Beta-amyloid PET ligands are a new and innovative technology that became clinically available for the first time in 2012 following FDA approval of Amyvid™ (Florbetapir F 18 Injection).[1] As the evidence summarized within this document demonstrates, with this new class of radioactive diagnostic agents clinically available, physicians need no longer wait until autopsy to identify beta-amyloid neuritic plaques in the brains of their patients who are being evaluated for potential Alzheimer's disease and can instead identify this disease

hallmark, or lack thereof, in life to enable intended changes in patient management plans[2] based on more accurate diagnoses and more appropriate therapies.

We request that CMS update Section 220.6 of the Medicare National Coverage Determination Manual to authorize appropriate Medicare coverage for the use of Positron Emission Tomography (PET) with a beta-amyloid detecting ligand as a diagnostic test for the purpose of estimating beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline. Determination of a patient's cognitive decline and plan of evaluation should be established by the treating physician, in accordance with the medical guidelines summarized later in this document. Beta amyloid PET scans should not be used as screeners in asymptomatic patients, on patients that have no documentation of cognitive decline, or on patients that present with symptoms and clinical profiles that make diagnosis clear and confident without the scan in the judgment of the treating physician. Additionally, the evidence does not currently support: the use of a positive beta-amyloid scan to establish a diagnosis of AD or other cognitive disorder; the use of a beta-amyloid scan to predict the development of dementia or other neurologic condition; or the use of beta-amyloid scans to monitor potential patient responses to therapies. We believe that recognition of these limitations on the use of beta-amyloid PET scans will permit CMS to target access to beta-amyloid PET scan to those patients for whom the evidence demonstrates the highest likelihood of diagnostic benefit.

This request highlights the current evidence for beta-amyloid imaging and the impact this class of PET scan tracers may have on intended patient management, and the potential positive impacts intended changes in patient management could have on patients, caregivers, and the Medicare program. The emergence of the first clinically-available PET agent for amyloid imaging fills a notable gap and unmet need within the medical community and demonstrates the importance of reconsidering Medicare's current NCD to enable appropriate adoption and application within a guideline-driven and defined patient population.

In addition to the formal request and supporting evidence, this submission includes:

- Appendix A: United States Package Insert (USPI) for Amyvid (Florbetapir F 18 Injection)
- Appendix B: Summary of Clinical Trials Supporting Amyvid Labeled Indication
- Appendix C: References

The information and statements contained in this letter are not intended for any promotional purpose whatsoever. This letter is solely a communication to CMS regarding information that may be relevant to the coverage of PET scans using beta-amyloid imaging agents. This information has been supplied as contemplated by CMS' guidance on NCD requests. Providers should not base decisions regarding whether to use Lilly's FDA approved beta-amyloid imaging agent Amyvid based on the information contained in this letter. Amyvid has only been approved for:

> "Positron Emission Tomography (PET) imaging of the brain to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition;a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations.
>
> Limitations of Use:
> • A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder.
> • Safety and effectiveness of Amyvid have not been established for:
> Predicting development of dementia or other neurologic condition;
> Monitoring responses to therapies."[3]

Lilly refers the reader to Amyvid's FDA approved label for full prescribing information.

Design, Purpose, and Method of Using Beta-amyloid PET Tracers

Design

Beta-amyloid tracers are small molecule agents radiolabeled with [18F] fluorine (F 18) that decays by positron (β+) emission to O 18. The principal photons useful for diagnostic imaging are the coincident pair of 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron.

Purpose

Beta-amyloid PET scan tracers are used to estimate beta-amyloid neuritic plaque density in adult patients as an adjunct to other diagnostic tests in patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative beta-amyloid PET scan: indicates sparse to no neuritic plaques, is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition, and reduces the likelihood that a patient's cognitive impairment is due to AD. A positive beta-amyloid PET scan indicates moderate to frequent amyloid neuritic plaques. Neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. As such, a positive beta-amyloid PET scan does not establish a diagnosis of AD or other cognitive disorder and is adjunct to other diagnostic evaluations.

Method of Use

Beta-amyloid PET scan tracers are intended for exclusive use by trained health care practitioners. A PET image should be acquired following intravenous injection of the beta-amyloid tracer. The patient should be supine and the head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Scans should then be displayed using a black-white scale with the maximum intensity of the scale set to the maximum intensity of all the brain pixels and interpreted using a binary visual read methodology. Images are designated as positive or negative by comparing the radioactivity in cortical gray matter with activity in the adjacent white matter. Images should only be interpreted by readers who successfully complete a special training program.

Regulatory and Coverage Background

Food and Drug Administration (FDA)

In June 2004, FDA published guidance on developing medical imaging radiopharmaceuticals. The FDA has stressed that new imaging agents (including PET radiopharmaceuticals) must demonstrate accuracy and reliability through clinical trials, thereby leading to improvements in the strength of clinical data available to support that the new generation of approved PET radiopharmaceuticals are accurate and reliable for imaging the desired targets. In addition, the FDA also now requires PET radiopharmaceuticals to demonstrate meaningful clinical utility. The FDA recognizes that in the absence of clinical usefulness, imaging agents can be harmful and should not be approved. By factoring in potential risks into its approval decision, FDA has provided an important and informed perspective on how to demonstrate or test clinical usefulness in defined populations and support a positive risk / benefit ratio. This strengthened requirement of the FDA creates confidence that new PET radiopharmaceuticals will not only be accurate and reliable, but also will have defined and accepted clinical benefits for the patients in whom they are used as specified in the FDA-approved label.

Amyvid (florbetapir) was approved by the FDA on April 6, 2012, and indicated "…for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations. Limitations of Use – A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder; Safety and effectiveness of Amyvid have not been established for: Predicting development of dementia or other neurologic condition; Monitoring responses to therapies."[4] Amyvid is the first clinically-available radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate beta-amyloid neuritic plaque density, though similar agents have been available previously within an "in research-only" capacity. The complete United States Package Insert (USPI) for Amyvid is included in Appendix A and includes all safety, efficacy, and indication information as required for a formal coverage request. While this request can provide coverage for any beta-amyloid PET tracer, it is also

consistent with the indication and population specified by the Amyvid label, the only example of a beta-amyloid label to date.

Centers for Medicare & Medicaid Services (CMS)

The medical necessity of PET technology in the diagnosis and clinical management of dementia has been previously determined by CMS. CMS conducted an extensive review of the uses of FDG-PET for the differential diagnosis of Alzheimer's disease and frontotemporal dementia between 2001 and 2003.[5] In 2004, CMS issued a positive coverage decision, NCD 220.6.13, which concluded that FDG-PET was "…reasonable and necessary in patients with a recent diagnosis of dementia and documented cognitive decline of at least six months, who meet diagnostic criteria for both Alzheimer's disease (AD) and frontotemporal dementia (FTD)."[6] The same NCD also contains a second and broader option that covers FDG-PET in the diagnosis of dementia under Coverage with Evidence Development. Together, the two forms of coverage for dementia in NCD 220.6.13 demonstrate CMS's recognition of the value of accurate differential diagnosis in the clinical management of dementia, as well as recognition that ongoing advances in PET-based neuroimaging are likely to benefit patients. We believe that these earlier refinements support the coverage we seek herein.

Within that same coverage decision CMS stated that, "…[a]ll other uses of FDG PET for patients with a presumptive diagnosis of dementia-causing neurodegenerative disease…for which CMS has not specifically indicated coverage continue to be noncovered."[7] CMS has publically stated its view that this statement ensured that additional uses of FDG PET remained non-covered and exclusionary language in the preamble to NCD 220.6 excludes all existing or future non-FDG tracers from coverage as well, even if those agents did not exist at the time of the review. Importantly, however, NCD 220.6.13 itself, by title and content, applies only to FDG PET, a very distinct technology when compared to PET scanning using a beta-amyloid identifying agent. Therefore, it would be inappropriate for CMS to use the existing coverage determination for FDG PET as the sole basis for analyzing or providing coverage for beta-amyloid tracers.

As we have noted above, there was no reason to include coverage of non-FDG tracers for dementia neuroimaging coverage in 2004, because any such tracers were many years from FDA approval. Today, a new and FDA-approved agent for the estimation of beta-amyloid plaque density via PET imaging has been approved. Therefore, it is both appropriate and necessary for new specific PET tracers to be covered for the appropriate Medicare patient populations and medical settings at this time.

The Medicare Statute provides Medicare coverage and reimbursement for services unless they are "not reasonable and necessary" for the diagnosis or treatment of a patient.[8] Amyloid imaging represents a new option to assist in the diagnosis of cognitively impaired patients who are being evaluated for Alzheimer's disease and other causes of cognitive decline. Indeed, a recent study that is currently pending publication (described in further detail below)[9], as well as additional published and ongoing studies summarized below, demonstrate that the use of PET imaging to identify beta-amyloid plaques in patients' brains can substantially impact a clinician's diagnostic decision making and intended management planning. Accordingly, it is our opinion that beta-amyloid PET agents meet the criteria of being both reasonable and necessary for use in patients being evaluated for cognitive impairment. The fact that these agents are not treatments for any specific disease is not relevant to their coverage and reimbursement under the Medicare program, as the statute provides for coverage for items or services which are reasonable and necessary in the diagnosis or treatment of a patient.[10]

Epidemiology

Alzheimer's Disease, Dementia, and Cognitive Impairment

The estimated prevalence of dementia among individuals aged 71 and older is 13.9%.[11] Contemporary dementia research has progressed rapidly on multiple fronts, including epidemiology, pathology, diagnosis, and treatment.[12] As a result, four primary dementia etiologies have been defined according to clinical and research criteria: 1) Alzheimer's disease (AD; including mixed-AD); 2) vascular dementias (VaD; including large and small vessel disease); 3) frontotemporal dementias (FTD; including Pick's disease, progressive nonfluent aphasia, and semantic dementia); and 4) dementia with Lewy bodies (DLB; including Parkinson's disease dementia [PDD]).[13] AD is the most common cause of dementia and accounts for 60-80% of all dementias in the United States.[14] However, this might be an overestimate because other causes of dementia share common features with AD and are often misdiagnosed as AD.[15]

Currently, one out of every 8 people aged 65 and older in the United States – or 5.2 million – has AD, with an estimated total of 5.4 million Americans with AD across all age groups.[16] Advancing age is the strongest risk factor for AD, with age-specific prevalence nearly doubling every 5 years beyond the age of 65.[17] Of patients with AD, an estimated 4% are under the age of 65, 6% are between the ages of 65 and 74, 44% are between the ages of 75 and 84, and 46% are age 85 and older.[18] As the number of older Americans grows, so too will the numbers of new and existing cases of AD and other dementias. According to projections by Hebert et al, by 2030 the number of people aged 65 and older with Alzheimer's disease is estimated to reach 7.7 million — a 50 percent

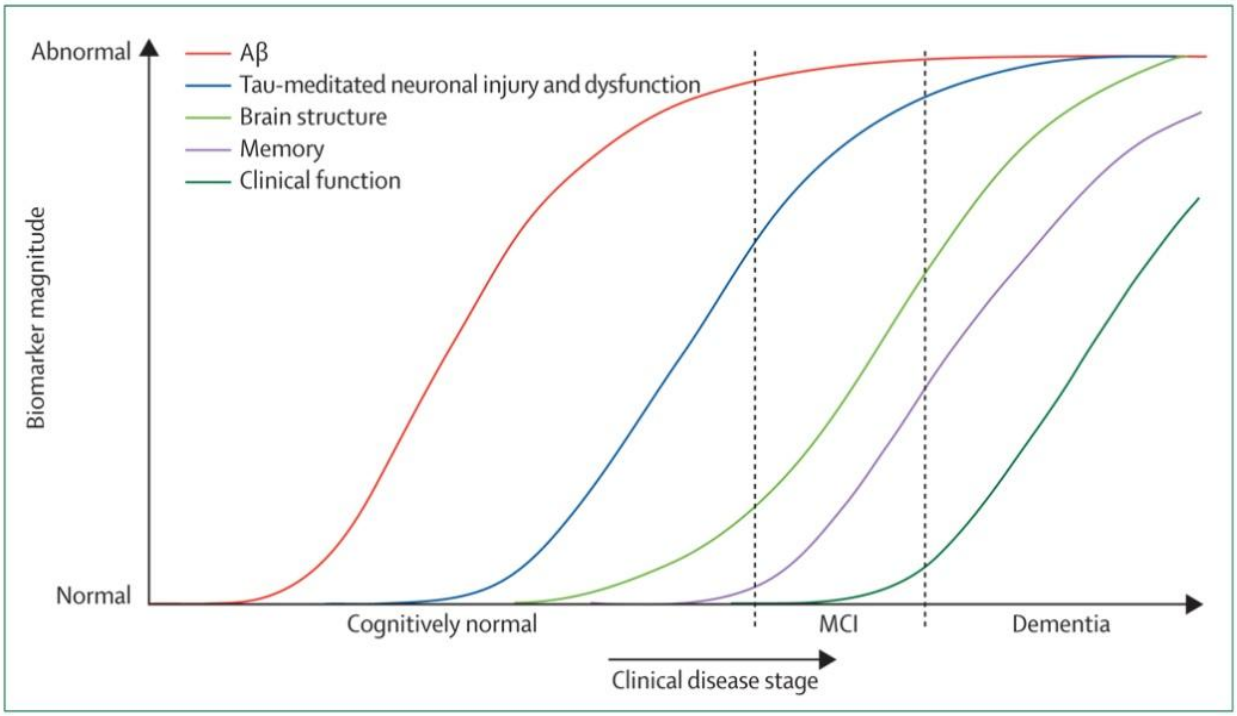
increase from the 5.2 million aged 65 and older currently affected and by 2050 the number may triple to a projected 11.3 to 16 million barring the development of medical breakthroughs to prevent or more effectively treat the disease.[19]

Although the prevalence of dementia and its associated disability increase exponentially with age, the focus of research has recently shifted towards the early stages of cognitive decline, namely MCI.[20] The pre-dementia (MCI) phase has been identified as the intermediate between normality and dementia.[21] On average, those with MCI convert to AD at a rate of about 10% to 25% annually compared to healthy elderly controls who convert at about 1% to 2% annually.[22] Of MCI patients, 20% progress to other dementia types but 30-40% of cases do not progress to dementia.[23]

Beta-amyloid

Current theories of AD pathophysiology hold that beta-amyloid deposition may begin years in advance of the onset of dementia.[24,25,26] Neuroimaging to detect beta-amyloid using PET has been widely researched in the past decade for the evaluation of Alzheimer's disease and other dementias. Amyloid imaging has potential as a diagnostic tool because it directly detects a core feature of the molecular pathology of AD.[27] This stands in contrast to other diagnostic imaging techniques, which detect the downstream effects of pathology on the brain, such as synaptic dysfunction (FDG-PET) and neuronal loss (MRI), which are thought to occur later in the disease cascade.[28] Biomarkers of beta-amyloid are indicative of upstream events that occur in the disease process.[29] Because accumulation of beta-amyloid in the brain is an early, disease-defining event (i.e., it is a sina qua non for definitive AD at autopsy), an *in vivo* test that can indicate the presence or absence of abnormal levels of beta-amyloid in the brain[30], could, when negative, help rule out AD as a potential clinical diagnosis.

Figure 1. Hypothesized beta-amyloid accumulation and clinical symptom progression in AD[31]



The challenges of differential diagnosis may improve with accurate information on brain plaque burden, since, for example, moderate to frequent amyloid plaques are present in AD patients, while PDD and FTD patients are distinguished by little or no plaques.[32] Since neuritic plaques are a defining feature of AD, knowing a patient lacks moderate to frequent neuritic plaques (as indicated by a negative amyloid scan) can help make this diagnosis less likely, and a physician can instead focus on pursuing other diagnoses, such as PDD or FTD.

The ^{11}C-labeled Pittsburgh compound B (^{11}C-PiB) was the first PET ligand to selectively visualize beta-amyloid in living patients.[33] A recent study by Rabinovici et al found that ^{11}C-PiB performed as well as FDG-PET, having the additional advantages of higher sensitivity, and better accuracy and precision of qualitative reads; it also slightly outperformed FDG-PET in patients with known histopathology.[34] However, the 20-minute half-life of ^{11}C-PiB limits its use to research centers equipped with a cyclotron and precludes widespread clinical application.[35] As the first PET ligand to image beta-amyloid *in vivo*, ^{11}C-PiB has been more widely studied than any of the radiopharmaceuticals that have followed. A recent review by Klunk cited 16 studies published from 2006-2010 that compared AD dementia patients with cognitively normal controls using ^{11}C-PiB PET scans,[36] while a separate analysis by Sojkova and Resnick identified ten (10) additional studies between 2004-2008 that examined ^{11}C-PiB

retention values in older adults without cognitive impairment, with mild cognitive impairment, and those with Alzheimer's disease.[37] More recently, a second generation of amyloid tracers with longer half-life (110 minutes vs. 20 minutes) have been developed, making it feasible to produce and distribute amyloid tracers for clinical use.[38]

Current Professional Standards for Diagnosing Alzheimer's Disease

Establishing a Pathological Diagnosis

Currently, AD is clinically diagnosed as "probable" or "possible" AD based on the presence of progressive cognitive impairment with insidious onset of sufficient severity to interfere with activities of daily living as well as absence of other neurological conditions that could account for the observed impairment.[39] Pathological diagnosis of AD is possible only after histopathological verification of the presence of beta-amyloid (Aβ) plaques (and typically neurofibrillary tangles) from brain tissue, using standardized criteria as described by Braak and Braak, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), the National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease (NIA-Reagan criteria), and the National Institute on Aging–Alzheimer's Association Guidelines for the Neuropathologic Assessment of Alzheimer's disease.[40,41,42,43]

Existing Guidelines for Clinical Diagnosis

Until recently, the clinical diagnosis of AD has relied mainly on guidelines developed jointly by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[44,45] More recent consensus guidelines for the diagnosis of AD have been published by the International Working Group for New Research Criteria for the Diagnosis of Alzheimer's disease[46] and through a joint effort of the National Institute on Aging and Alzheimer's Association[47]. The diagnostic process typically starts with the patient or caregiver visiting the primary care provider to present initial complaints of symptoms. Cognitive function assessments include the Mini-Cog test, the General Practitioner Assessment of Cognition (GPCOG),[48] and the Mini-Mental State Examination (MMSE); MMSE remains the most widely used cognitive test instrument.[49,50] The diagnostic workup also includes neuropsychological examinations, which can be aided by neuropsychological tests. These assessments are useful for identifying people who require more comprehensive testing, but are insufficient to establish a clinical diagnosis of dementia.[51]

Laboratory tests and structural neuroimaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), are typically ordered to rule out the presence of treatable disorders presenting as memory loss, such as renal failure, brain tumor, normal pressure

hydrocephalus and subdural hemorrhages.[52] Basic blood tests typically include complete blood count, thyroid stimulating hormone, serum calcium, electrolytes, and fasting glucose. Other selective testing, such as serum vitamin B12 and folate levels, rapid plasma reagin for syphilis screening, and HIV antibodies, has also been recommended.[53]

Recommendations for Appropriate Use of Beta-amyloid Imaging Agents Are Under Development

At the time this request was submitted, we were aware that new appropriate use recommendations for the use of beta amyloid imaging agents were being developed by the Alzheimer's Association in partnership with the Society of Nuclear Medicine, as well as similar efforts by the International Working Group for New Research Criteria for Alzheimer's Disease. We anticipate that the Alzheimer's Association/SNM recommendations will be finalized and released during the course of any National Coverage Analysis that is opened subsequent to this request. While we do not know the content of these pending recommendations, these stakeholders are widely accepted as leaders in developing and identifying best practices for patients within this space and we strongly urge CMS to consider their offerings as a model for defining appropriate and reasonable standards for use.

Unmet Need in Alzheimer's Disease Diagnosis

The diagnosis and treatment of AD have been hampered by the absence of reliable non-invasive biomarker measurements of the underlying pathology antemortem[54]. Even after testing, the diagnosis may remain uncertain and an inappropriate trial and error approach to medications may be used, or the passage of time may cause symptoms to either resolve or worsen.

Bradford et al[55] conducted a systematic review of the literature to determine the prevalence and contributing factors for missed, incorrect and delayed dementia diagnosis in primary care. Of 791 people who met standard diagnostic criteria for dementia, 384 had the diagnosis recorded in their medical record or reported by the examining physician, representing a diagnostic sensitivity of 49%. The likelihood of receiving a diagnosis of dementia depended on the severity of dementia where 60-100% of patients with severe dementia were diagnosed as compared with 9-41% of mild dementia.

The Quality Standards Subcommittee of the American Academy of Neurology conducted an evidence-based review of literature published from 1985 through 1999 to evaluate the effectiveness of dementia diagnosis guidelines as compared to the standard of pathology at autopsy.[56] Clinical diagnosis of AD in most centers was only 81% sensitive (range 49% to 100%) and 70% specific (range 47% to 100%) for "probable" AD, where the majority of studies showed either good sensitivity at the expense of specificity, or vice versa.

Additionally, a diagnosis of "possible" AD achieved a sensitivity of 93% (range 85% to 96%) but a specificity of only 48% (range 32% to 61%). Additional published studies have reported similar results.[57,58,59,60]

An updated analysis from the Honolulu-Asian Aging Study (HAAS)[61,62] showed that, while 56% of a cohort of 363 demented subjects were clinically diagnosed with AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorder Association criteria for AD[63] during life, only 19% met the stringent AD pathological criteria (CERAD or Braak Stage V/VI) at autopsy.[64,65] Another 27.5% of subjects were found to have a dominant microvascular pathology, while 20.5% were judged to have codominant AD and microvascular pathology. Mok et al reported concordance between dementia diagnoses and autopsy findings for primary care physicians versus neurologists from one AD Research Center.[66] The overall diagnostic accuracy was 81%; 84% for non-neurologists and 77.5% for neurologists (p = 0.125). For AD, non-neurologists had a diagnostic concordance rate of 91% and neurologists 87% (p=0.07).

Misdiagnosis can have serious ramifications for patients. If a patient with frontotemporal dementia is misdiagnosed with AD, for example, acetylcholinesterase inhibitors can lead to exacerbation of symptoms.[67] A misdiagnosis of AD for a patient with dementia with Lewy bodies (DLB) may result in s*evere side effects or fatal complications* if behavioral symptoms are treated with antipsychotic drugs.[68] Patients with DLB are particularly sensitive to developing extrapyramidal symptoms (EPS) as well as the potentially fatal complication of neuroleptic sensitivity, which affects approximately 50% of DLB patients.[69] Thus, false positive diagnoses may lead to unnecessary treatment, worsening of patient outcomes, and inefficient or inappropriate use of health care resources; all aspects of medical care CMS has an expressed interest in controlling and could be better able to do so using an *in vivo* beta-amyloid PET scan to rule out AD etiology.

Beta Amyloid Identifying Tracers for Use with Positron Emission Tomography (PET)

Clinical Evidence That Demonstrates the Efficacy of Beta Amyloid PET Tracers

During the past five years, amyloid imaging has established itself as an important neuroimaging tool for the investigation of brain aging and dementia.[70] Several PET ligands have now been developed that demonstrate high affinity for amyloid plaques. *In vitro* studies have shown that PET imaging ligands such as ^{11}C-PiB (Pittsburgh Compound-B),[71,72] ^{18}F-florbetaben[73,74] and Amyvid (^{18}F-florbetapir),[75] bind to beta-amyloid and co-localize with

plaques stained by thioflavin and other amyloid labeling agents. A fourth agent, ^{18}F-flutemetamol, is the 3' fluoro-analogue of ^{11}C-PiB.[76] The first direct visualization of brain amyloid using ^{11}C-PiB was demonstrated in 16 patients with mild AD, whose uptake patterns were consistent with amyloid plaque deposition reported in autopsied AD brains.[77]

However, a definitive demonstration of the relationship between PET amyloid imaging and brain beta-amyloid burden requires a comparison between *in vivo* imaging and brain pathology, usually at autopsy, in the same patient. Six single-subject/single-center studies used ^{11}C-PiB PET compared to pathological examination. Two studies described patients with clinical diagnosis and autopsy confirmation of DLB, who had amyloid positive ^{11}C-PiB PET scans in life, but borderline beta-amyloid pathology at autopsy.[78,79,80,81] Ikonomovic et al reported strong correlations (0.7 to 0.8) between regional ^{11}C-PiB PET tracer uptake and various postmortem measures of beta-amyloid burden.[82] Cairns et al reported a 91 year old with clinical diagnosis of early AD with a negative ^{11}C-PiB PET scan but reduced CSF beta-amyloid.[83] The autopsy revealed numerous diffuse plaques, but sparse cored plaques and isolated neurofibrillary tangles, and the neuropathologic diagnosis was borderline as low probability of AD by NIA Reagan criteria, and possible AD by CERAD criteria.[84] However, the ^{11}C-PiB PET scan was taken more than two years prior to autopsy and may indicate either a failure of the ^{11}C-PiB PET scan to detect an early stage of AD, or accurate negative due to lack of convincing AD pathology. Leinonen et al reported that 5/10 subjects who had a tissue removed for a shunt for NPH had significant numbers of beta-amyloid aggregates by immunohistochemistry (IHC) at biopsy, where four of these subjects had abnormal ^{11}C-PiB scans.[85] The overall correlation between ^{11}C-PiB uptake in the right frontal cortex with the amount of amyloid aggregates in the right frontal cortical biopsy specimens across the 10 subjects was 0.85. Wolk et al undertook a similar study using ^{18}F-flutametamol (an ^{18}F-labeled analogue of ^{11}C-PiB) with similar results. In 7 patients who underwent tissue removal in association with shunt placement for NPH, cortical tracer uptake correlated with the biopsy tissue amyloid burden as assessed by IHC.[86]

Studies using Amyvid (^{18}F-florbetapir) have also examined the link between PET imaging and underlying beta-amyloid burden. Amyvid PET signal correlates with clinical diagnosis, age, and apolipoprotein E (ApoE) genotype; variables known to be associated with increased prevalence of underlying beta-amyloid pathology.[87]

Clark et al recently reported the first prospective multicenter Phase 3 study to evaluate the relationship between cortical amyloid burden measured on PET scan and true beta-amyloid burden assessed by postmortem histopathology.[88] There is a strong, statistically significant correlation between the level of cortical tracer uptake in Amyvid PET scan image and true overall beta-amyloid burden on subsequent autopsy ($\rho = 0.71$ to 0.78, $p<0.0001$) in the 29

(primary analysis cohort) of 35 cognitively normal, MCI, AD and other dementia patients that went to autopsy.[89]

Studies of Amyvid have demonstrated the ability to characterize cortical beta-amyloid burden levels in patients and determine whether an image is associated with moderate to frequent neuritic plaques.[90] The evaluation of Amyvid PET using a binary reading method has been carried out in three separate blinded reader studies (A08, A16, and PT01), in which 19 total readers were trained and 1365 individual reads were reviewed.[91] With an expanded dataset, the A16 study utilized a majority read assessment to evaluate the effectiveness of Amyvid PET in appropriately identifying beta-amyloid in the brain. Within the entire dataset of 59 patients, the sensitivity using the majority interpretation of the readers was 92% (95% CI: 78% to 98%) and specificity was 100% (95% CI: 80% to 100%)[92] for predicting moderate-to-frequent beta-amyloid neuritic plaques at autopsy.[93] Furthermore, the reliability of both in-person and web-based training of binary reading method for Amyvid PET have been studied (see Table 1), with reliability measures from the most recent web-based study demonstrating an overall Fleiss' kappa value of 0.83[94]. Measures of accuracy within that same study showed median sensitivity = 82% and median specificity = 95%, based on histopathological truth standard.[95]

Table 1. Median Sensitivity and Specificity of Amyvid PET*[96]

	A08 (N=35)	**A16 (N=59)**	**PT01 (N=59)**
Sensitivity	100% (84%-100%)	92% (69%-95%)	82% (69%-92%)
Specificity	94% (69%-100%)	95% (90%-100%)	95% (90%-95%)
Training program	In Person	In Person	Online

*Percentage range in parenthesis reflects min/max across individual readers

Together, these results supported the FDA approval of Amyvid for estimating brain neuritic plaque density by providing evidence that beta-amyloid PET tracers can provide an accurate and reliable *in vivo* estimate of underlying amyloid pathology.

Further details and summaries of all clinical trials included within the Amyvid USPI are available in Appendix B.

Evidence Supporting the Effectiveness (Value) of Beta Amyloid PET Tracers for CMS Coverage

There remains a need for improved diagnostic accuracy for neurodegenerative disease to enable differential diagnosis of patients presenting with cognitive impairment or dementia. In each of these situations there is great value to having a negative beta-amyloid scan because a disease diagnosis associated with the presence of beta-amyloid can be made less likely and the focus of patient management, including medications, can be redirected and administered in a more targeted way. Differential diagnosis is enhanced by amyloid scans where, for example, the levels of amyloid are comparable in dementia with Lewy bodies (DLB) and AD, while Parkinson Dementia and FTD are distinguished by little or no amyloid.[97] Global cortical amyloid burden as measured by ^{11}C-PiB is high in DLB and AD but low in normals, and Parkinson disease patients with or without dementia.[98]

The potential value of biomarkers for AD diagnosis has been recognized in recent consensus publications as well.[99,100,101,102] While the majority of these publications only consider amyloid biomarkers within research settings, it is important to note that at the time they were written, no such biomarkers existed for clinical use. Similarly, the existing consensus criteria for AD diagnosis began incorporating beta-amyloid PET scan biomarkers into diagnostic algorithms before they were clinically available as well. Regardless, each of these consensus publications points to a new and growing utility in clinical diagnosis provided by *in vivo* beta-amyloid biomarkers such as PET scans with an amyloid imaging agent. A succinct summary on this topic was offered by the International Working Group for New Research Criteria for the Diagnosis of Alzheimer's disease in 2010 stating: "...we anticipate that in the future a single in-vivo marker or, more likely, a combination of markers might be as reliable as neuropathological criteria in establishing a definite diagnosis of AD."[103] We acknowledge that the clinical evidence at this time does not support use of a beta-amyloid imaging agent as an in-vivo marker to replace neuropathological criteria in establishing a definitive diagnosis of AD. With the FDA's approval of the first of these agents for clinical use, future guidelines – such as those mentioned previously being developed by a mutli-stakeholder group led by the Alzheimer's Association and the Society for Nuclear Medicine – will need to address how to translate the best practices for the use of these innovative biomarkers that were previously limited to research settings into meaningful clinical use.

The value of knowing the diagnosis provides both clinical management and intrinsic value, including enhanced patient and physician satisfaction resulting from increased knowledge. The Alzheimer's Association summarizes the problem of a delayed diagnosis in their Facts and Figures for 2011: "Delayed detection of AD or other dementia, or delayed or missed diagnosis, deprives affected people of numerous potential benefits and imposes unnecessary physical and emotional burdens on their caregivers."[104] The Association expanded on this

same finding within its Facts and Figures 2012 publication, noting the detrimental impacts of delayed detection can include: "Lost opportunities to manage symptoms; potential misuse of medications that may worsen cognitive function; missed opportunities to manage coexisting medical conditions that may worsen cognitive function; …missed opportunities to prevent falls and injuries, including potentially fatal injuries; [and]…delays in planning for future functional declines."[105] As noted previously within this document, it is possible amyloid imaging could help improve the diagnostic accuracy of physicians in making a diagnosis of an AD or a non-AD dementing process, in-turn helping patients make more informed decisions about their future.

The impact of the diagnostic imaging information on a physician's intended patient management has been previously proposed by members of CMS' Coverage and Analysis Group (CAG) as a meaningful endpoint for evaluating the value of that diagnostic, a concept that is also supported within the available literature[106]. Indeed, in a recent study by Rowe and Villemagne the potential of this impact became even more pronounced when they reported that, "…commencing therapy in MCI without other evidence to support the presence of prodromal AD will lead to inappropriate medication use in about 50% of cases."[107] There exists a clear need to supply clinicians with accurate beta-amyloid biomarker information in order to ensure that that those without AD pathology are identified as early as responsibly possible, thereby avoiding the inappropriate medication use Rowe and Villemagne noted.

Study A13[108] (presented here as data on file pending publication) was a preliminary test of whether information from an Amyvid PET scan could change an expert clinician's diagnosis. In this study, 44 Amyvid PET scans – split evenly between patients entering with an enrolling physician diagnosis of either mild cognitive impairment or Alzheimer's disease – were reviewed by three independent expert nuclear medicine physicians. The three physicians provided an initial patient management plan while blinded to the subject's initial clinical diagnosis and the patient's Amyvid PET imaging results. Once physicians were presented with the Amyvid PET scan for those same patients, experts changed their diagnosis in 85% of the cases (range 66-100%) on the basis of an indeterminate disease origin or a previous diagnosis that was inconsistent with PET scan results. Overall, the three physicians provided a diagnosis at post-test that was consistent with the Amyvid PET scan results 87% of the time, and two of the three provided diagnoses consistent with Amyvid PET 95% and 98 % of the time, respectively. For the entire group of 44 cases, the three expert clinicians altered specific components of their management plan in 80% of the cases they reviewed (range 75-84%, $p < 0.0001$) as a result of the information provided by the Amyvid PET scan (Table 2).

Table 2. Effect of Amyvid PET Scan Results on Management Decisions[109]

Management	Positive scan (n=66)		Negative scan (n=66)	
	Pre	Post	Pre	Post
Give a trial of an AChEIs or memantine	19 (28.8%)	38 (57.6%)	17 (25.8%)	1 (1.5%)
Extensive neuropsychological testing	19 (28.8%)	8 (12.1%)	16 (24.2%)	33 (50.0%)
FDG-PET	6 (9.1%)	2 (3.0%)	11 (16.7%)	30 (45.5%)
Lumbar puncture	20 (30.3%)	1 (1.5%)	20 (30.3%)	17 (25.8%)
Evaluate vascular disease	3 (4.5%)	1 (1.5%)	2 (3.0%)	10 (15.2%)
Evaluate DLB/FTD/PSP/CBGD/Aphasia/etc	1 (1.5%)	0 (0.0%)	4 (6.1%)	6 (9.1%)

In addition to the evidence summarized above, at the time of this submission there is an active and ongoing study – ClinicalTrials.gov Identifier: NCT01400425; Protocol Number ^{18}F-AV-45-A17; *Potential of Florbetapir F 18 PET to Inform Clinical Diagnosis and Management of Patients with Progressive Cognitive Decline* (or A17, for short) – designed to test the potential for Amyvid PET to change patient's clinical diagnosis and management plan. Since a negative scan suggests the absence of amyloid pathology and such pathology is required for a definitive diagnosis of AD, a negative Amyvid PET scan can provide evidence against an AD diagnosis.

In this context, A17 is designed to evaluate whether an Amyvid PET scan can impact the diagnostic thinking when physicians are making a diagnosis for the likely cause of a Medicare-eligible subject's progressive cognitive impairment in approximately 200 patients who have either recently completed a comprehensive clinical evaluation for progressive cognitive decline or who are currently being evaluated for progressive cognitive decline. Eligible subjects will be referred by the site physician to an imaging facility to undergo an Amyvid PET scan. Subjects will undergo screening assessments prior to the Amyvid PET scan that will include the collection of demographic information, medical history and current medications, vital signs, and a Mini-Mental State Exam (MMSE). In addition to these evaluations, the site physician will indicate his or her current diagnosis and intended management plan as if the Amyvid PET scan were not being performed. The subject and subject's caregiver will be asked to complete pre-scan surveys as well. Upon reviewing the results of the Amyvid scan, the site physician will again indicate his or her current diagnosis and intended management plan, including any intended change since baseline. To isolate the effect of the Amyvid PET scan on a change (or lack thereof) in patient diagnosis and/or management, no further neuropsychological testing or laboratory tests may be completed

between the time the physician completes the screening form and the time he or she completes the post-scan form.

A17 is scheduled to complete enrollment very near the time of this coverage request, enabling the potential for analysis and peer-reviewed publication during 2012. Given this timeline, A17 will likely be published during the course of the National Coverage Analysis CMS would be undertaking pursuant to this request, and could thereby be considered as an additional, and potentially invaluable, piece of evidence that further demonstrates the value of beta-amyloid PET imaging to patients, physicians, and the Centers for Medicare and Medicaid Services.

Summary

The difficulties faced by physicians in diagnosing patients with cognitive impairment and the potential consequences of an incorrect and/or delayed diagnosis underscore the need for improved diagnostic tools and methods. As detailed above, a misdiagnosis can have negative consequences for patients who may receive treatment for a disease they do not have, while the disease from which the patient suffers potentially goes without appropriate treatment.

Recently, Congress passed the National Alzheimer's Project Act to "…build upon and leverage HHS programs and other federal efforts to help change the trajectory of [Alzheimer's disease and related dementias]."[110] The Department of Health and Human Services (HHS) has operationalized its response to this new initiative by creating a National Plan to Address Alzheimer's Disease, laying out five (5) goals considered of primary importance in meeting the needs of patients, families, physicians, and health systems suffering under the weight of Alzheimer's disease and related dementias (ADRD). Within that National Plan, HHS notes that ensuring patient access to timely and accurate diagnoses is a necessary step toward enhancing quality and efficiency of care patients receive. Specifically, HHS stated[111]:

> *Far too many people with Alzheimer's disease are not diagnosed until their symptoms have become severe.*[112] *Timely diagnosis gives people with the condition, and their families, time to plan and prepare for the future, leading to more positive outcomes for both.*[113,114] *…Even with access to affordable care for individuals, the health care workforce needs tools that can help ensure timely and accurate diagnoses. Research has helped identify some assessment tools that can be used to detect cognitive impairment that may indicate the need for a comprehensive diagnostic evaluation for Alzheimer's disease.*[115]

PET scans using a beta-amyloid binding tracer offer patients, physicians, and the health care system an innovative and appropriate adjunct to other diagnostic evaluations. Through the application of a negative beta-amyloid PET scan – and the resulting decreased likelihood of Alzheimer's disease being the likely underlying etiology of a patient's dementia – the entire medical system has the potential to benefit: clinicians have the information needed to potentially avoid the high rate of misdiagnoses noted above. This may allow patients and caregivers to be better able to plan and provide for the treatment of disease and may allow Medicare to ensure that patients receive only those medications and treatments that are appropriate, safe, and useful for the disease being treated. By ensuring patient access to this technology, we believe CMS can help move many who suffer from debilitating dementia-based diseases closer to the national goal of ensuring high quality care that makes a difference in patients' lives.

Based on the evidence presented here that demonstrates both a vital unmet medical need and an innovative technology indicated for this patient group to help address that need, we respectfully request that CMS reconsider its non-coverage decision of PET scans and provide coverage for the use of beta-amyloid PET scans as a diagnostic test for the purpose of estimating beta-amyloid neuritic plaque density in adult patients with documented cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline.

We welcome the opportunity to meet with you to discuss any of the evidence detailed herein, or to provide any additional information and research you believe will be helpful for your analysis. For convenience, please contact Craig Hunter, Senior Research Scientist, Eli Lilly & Company, at (317) 277-1211, or via email at craig.hunter@lilly.com.

Sincerely,

Daniel Skovronsky, MD, PhD
Global Brand Development Leader, Amyvid

Wei-Li Shao
Senior Director, Alzheimer's Business Unit

Derek Asay
Director, Government Strategy, Federal Accounts, and Quality

Appendix A:

United States Package Inserts (USPI) for Amyvid (Florbetapir F 18 Injection)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Amyvid safely and effectively. See full prescribing information for Amyvid.

Amyvid (Florbetapir F 18 Injection) for intravenous use

Initial U.S. Approval: 2012

INDICATIONS AND USAGE

Amyvid is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations (1).

Limitations of Use

- A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder (1).
- Safety and effectiveness of Amyvid have not been established for:
  - Predicting development of dementia or other neurologic condition;
  - Monitoring responses to therapies (1).

DOSAGE AND ADMINISTRATION

Use appropriate radiation safety handling measures (2.1).

- Administer 370 MBq (10 mCi) as a single intravenous bolus in a total volume of 10 mL or less (2.2).
- Obtain 10-minute PET images starting approximately 30 to 50 minutes after intravenous injection (2.3).
- Image interpretation: Refer to full prescribing information (2.4).
- The radiation absorbed dose from a 370 MBq (10 mCi) dose of Amyvid is 7 mSv in an adult (2.5).

DOSAGE FORMS AND STRENGTHS

10 mL, 30 mL, or 50 mL multidose vial containing a clear, colorless injectable solution at a strength of 500-1900 MBq/mL (13.5-51 mCi/mL) florbetapir F 18 at End of Synthesis (EOS) (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Image interpretation errors (especially false negatives) have been observed (5.1).
- Radiation risk: Amyvid, similar to all radiopharmaceuticals, contributes to a patient's long-term cumulative radiation exposure. Ensure safe handling to protect patients and health care workers from unintentional radiation exposure (2.1, 5.2).

ADVERSE REACTIONS

Most commonly reported adverse reactions were: headache (2%), musculoskeletal pain (1%), fatigue (1%), and nausea (1%) (6).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Amyvid is indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations.

Limitations of Use:

- A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder.
- Safety and effectiveness of Amyvid have not been established for:
  - Predicting development of dementia or other neurologic condition;
  - Monitoring responses to therapies.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety - Drug Handling

Amyvid is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure during administration *[see Warnings and Precautions (5.1)]*. Use waterproof gloves and effective shielding, including lead-glass syringe shields when handling Amyvid. Radiopharmaceuticals, including Amyvid, should only be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radioactive materials, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

2.2 Recommended Dosing and Administration Instructions

The recommended dose for Amyvid is 370 MBq (10 mCi), maximum 50 µg mass dose, administered as a single intravenous bolus in a total volume of 10 mL or less. Follow the injection with an intravenous flush of 0.9% sterile sodium chloride.

- Inspect the radiopharmaceutical dose solution prior to administration and do not use it if it contains particulate matter or is discolored.
- Use aseptic technique and radiation shielding to withdraw Amyvid solution.
- Assay the dose in a suitable dose calibrator prior to administration.
- Inject Amyvid through a short intravenous catheter (approximately 1.5 inches or less) to minimize the potential for adsorption of the drug to the catheter. Portions of the Amyvid dose may adhere to longer catheters.

2.3 Image Acquisition Guidelines

A 10-minute PET image should be acquired starting 30 to 50 minutes after Amyvid intravenous injection. The patient should be supine and the head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Image reconstruction should include attenuation correction with resulting transaxial pixel sizes between 2 and 3 mm.

2.4 Image Display and Interpretation

Amyvid images should be interpreted only by readers who successfully complete a special training program *[see Warnings and Precautions (5.1)]*. Training is provided by the manufacturer using either an in-person tutorial or an electronic process.

The objective of Amyvid image interpretation is to provide an estimate of the brain β-amyloid neuritic plaque density, not to make a clinical diagnosis. Image interpretation is performed independently of a patient's clinical features and relies upon the recognition of unique image features.

Image Display

Images should be displayed in the transaxial orientation with access as needed to the sagittal and coronal planes. In reviewing the images, include all transaxial slices of the brain using a black-white scale with the maximum intensity of the scale set to the maximum intensity of all the brain pixels. Initially locate the brain slice with the highest levels of image contrast (highest radioactivity signals for Amyvid uptake) and adjust the contrast appropriately. Start image interpretation by displaying slices sequentially from the bottom of the brain to the top. Periodically refer to the sagittal and coronal plane image display, as needed to better define the radioactivity uptake and to ensure that the entire brain is displayed.

Image Interpretation

Image interpretation is based upon the distribution of radioactive signal within the brain; clinical information is not a component of the image assessment *[see Warnings and Precautions (5.1)]*. Images are designated as positive or negative by comparing the radioactivity in cortical gray matter with activity in the adjacent white matter. This determination is made only in the cerebral cortex; the signal uptake in the cerebellum does not contribute to the scan interpretation (for example, a positive scan may show retained cerebellar gray-white contrast even when the cortical gray-white contrast is lost).

- *Negative scans* show more radioactivity in white matter than in gray matter, creating clear gray-white contrast.
- *Positive scans* show cortical areas with reduction or loss of the normally distinct gray-white contrast. These scans have one or more areas with increased cortical gray matter signal which results in reduced (or absent) gray-white contrast. Specifically, a positive scan will have either:
  a) Two or more brain areas (each larger than a single cortical gyrus) in which there is reduced or absent gray-white contrast. This is the most common appearance of a positive scan.

  or

  b) One or more areas in which gray matter radioactivity is intense and clearly exceeds radioactivity in adjacent white matter.

Some scans may be difficult to interpret due to image noise, atrophy with a thinned cortical ribbon, or image blur. For cases in which there is uncertainty as to the location or edge of gray matter on the PET scan and a co-registered computerized tomography (CT) image is available (as when the study is done on a PET/CT scanner) the interpreter should examine the CT image to clarify the relationship of the PET radioactivity and the gray matter anatomy.

Figures 1, 2, and 3 provide examples of negative and positive scans. Figure 1 demonstrates varying degrees of normal gray-white contrast (negative) and examples where gray-white contrast has been lost (positive). Figure 2 illustrates typical features of a negative scan, while Figure 3 shows the loss of gray-white contrast in different brain regions of a positive scan.

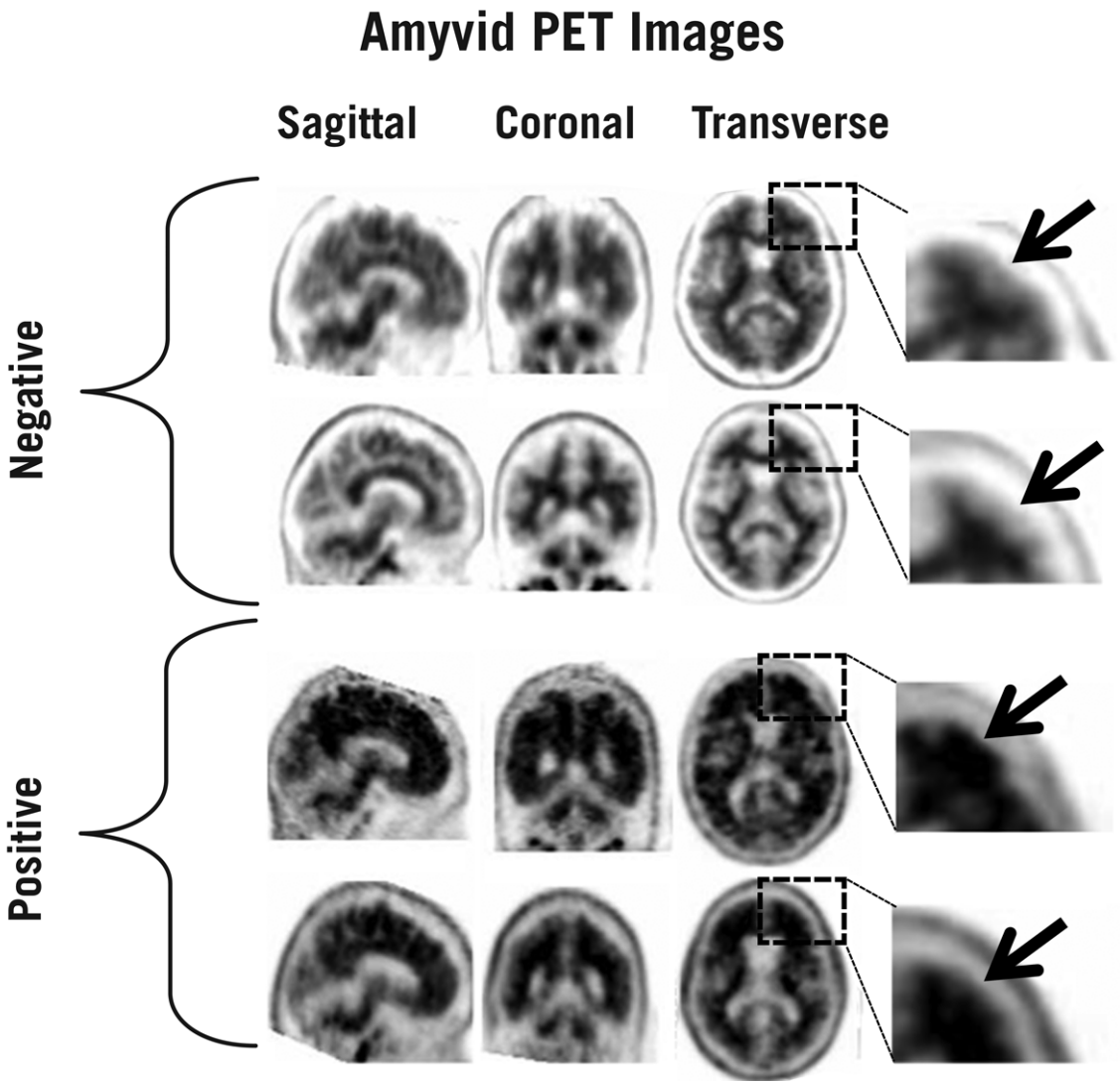


Figure 1: Examples of Amyvid negative scans (top two rows) and positive scans (bottom two rows). Left to right panels show sagittal, coronal, and transverse PET image slices. Final panel to right shows enlarged picture of the brain area under the box. The top two arrows are pointing to normal preserved gray-white contrast with the cortical radioactivity less than the adjacent white matter. The bottom two arrows indicate areas of decreased gray-white contrast with increased cortical radioactivity that is comparable to the radioactivity in the adjacent white matter.

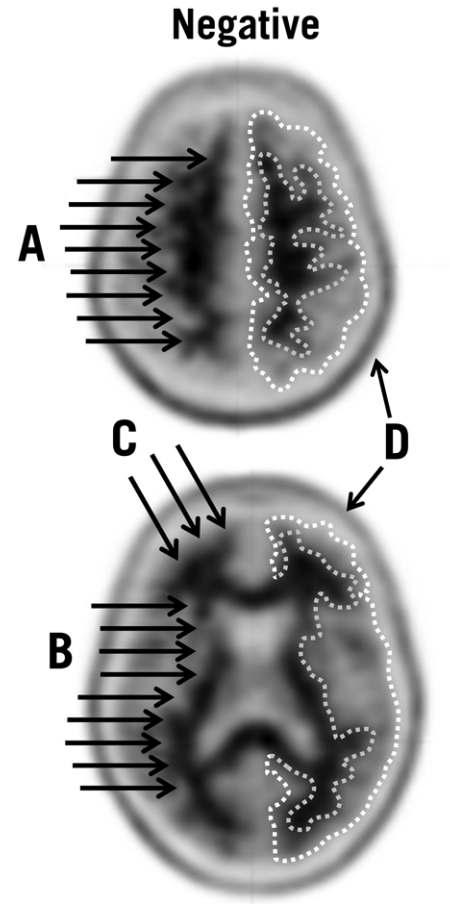


Figure 2: Typical Negative Scan. Images are displayed from a negative scan with upper (top) and lower (bottom) transverse slices both showing good gray-white matter contrast. On the right side of each slice, dotted lines have been used to illustrate the edge of the cortical gray matter (outer line) and the gray-white border (inner line). These dotted lines highlight contrast in uptake between the less intense uptake in the gray matter and the more intense uptake in the white matter. In addition, arrows illustrate the following points:

A) White matter tracts can be delineated from the frontal lobe to parietal lobe.

B) White matter tracts are clearly identified throughout the occipital / temporal area.

C) Scalloped appearance is seen with “fingers” of white matter in the frontal cortex.

D) Low levels of tracer in scalp or skull that should be distinguished from gray matter uptake by its shape and position.

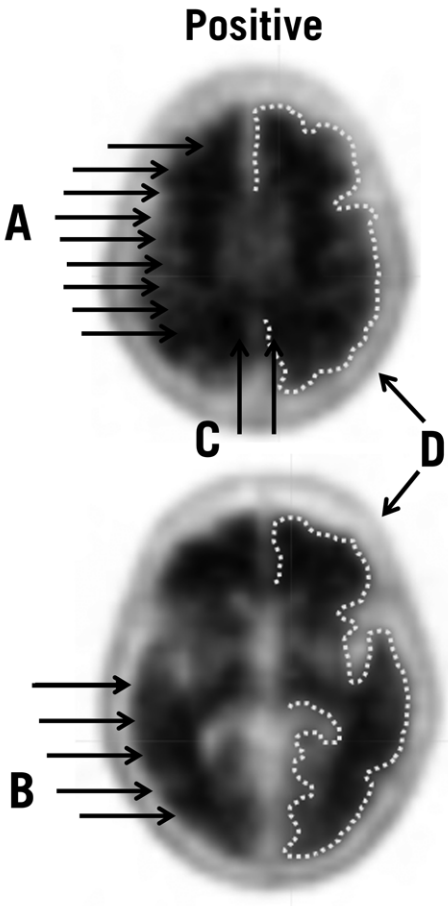


Figure 3: Typical Positive Scan: Images from a positive scan showing upper (top) and lower (bottom) transverse slices with loss of gray-white matter contrast in multiple brain regions. On the right side of each slice the edge of the cortical gray matter has been illustrated with a dotted line. Compared to the images from the negative case in Figure 2, the gray matter uptake is more similar to the white matter uptake and the gray-white matter border is more difficult to discern. In addition, arrows show the following points:

A) White matter tracts are difficult to fully identify as they travel from frontal to parietal lobe.

B) Borders of white matter tracts in occipital / temporal area are lost in places.

C) Gray matter in medial parietal cortex (precuneus) has increased uptake.

D) Low levels of tracer in scalp or skull that should be distinguished from gray matter uptake by its shape and position.

2.5 Radiation Dosimetry

The estimated radiation absorbed doses for adults from intravenous injection of Amyvid are shown in Table 1.

Table 1: Estimated Radiation Absorbed Dose, Amyvid (Florbetapir F 18 Injection)

ORGAN/TISSUE	MEAN ABSORBED DOSE PER UNIT ADMINISTERED ACTIVITY(µGy/MBq)
Adrenal	14
Bone - Osteogenic Cells	28
Bone - Red Marrow	14
Brain	10
Breasts	6
Gallbladder Wall	143
GI[a] - Lower Large Intestine Wall	28
GI - Small Intestine	66
GI - Stomach Wall	12
GI - Upper Large Intestine Wall	74
Heart Wall	13
Kidneys	14
Liver	64
Lungs	9
Muscle	9
Ovaries	18
Pancreas	14
Skin	6
Spleen	9
Testes	7
Thymus	7
Thyroid	7
Urinary Bladder Wall	27
Uterus	16
Total Body	12
Effective Dose (µSv/MBq)[b]	19

[a] Gastrointestinal

[b] Assumed radiation weighting factor, w_r, (formerly defined as quality factor, Q) of 1 for conversion of absorbed dose (Gray or rads) to dose equivalent (Sieverts or rem) for F 18. To obtain radiation absorbed dose in rad/mCi from above table, multiply the dose in µGy/MBq by 0.0037, (e.g., 14 µGy/MBq x 0.0037 = 0.0518 rad/mCi)

The effective dose resulting from a 370 MBq (10 mCi) dose of Amyvid is 7.0 mSv in an adult, (19 x 370 = 7030 µSv = 7.030 mSv). The use of a CT scan to calculate attenuation correction for reconstruction of Amyvid images (as done in PET/CT imaging) will add radiation exposure. Diagnostic head CT scans using helical scanners administer an average of 2.2 ± 1.3 mSv effective dose (CRCPD Publication E-07-2, 2007). The actual radiation dose is operator and scanner dependent. The total radiation exposure from Amyvid administration and subsequent scan on a PET/CT scanner is estimated to be 9 mSv.

3 DOSAGE FORMS AND STRENGTHS

Amyvid (Florbetapir F 18 Injection) is available in a 10 mL, 30 mL, and 50 mL multidose vial containing a clear, colorless solution at a strength of 500-1900 MBq/mL (13.5-51 mCi/mL) florbetapir F 18 at End of Synthesis (EOS).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk for Image Misinterpretation and other Errors

Errors may occur in the Amyvid estimation of brain neuritic plaque density during image interpretation *[see Clinical Studies (14)]*.

Image interpretation should be performed independently of the patient's clinical information. The use of clinical information in the interpretation of Amyvid images has not been evaluated and may lead to errors. Other errors may be due to extensive brain atrophy that limits the ability to distinguish gray and white matter on the Amyvid scan as well as motion artifacts that distort the image.

Amyvid scan results are indicative of the brain neuritic amyloid plaque content only at the time of image acquisition and a negative scan result does not preclude the development of brain amyloid in the future.

5.2 Radiation Risk

Amyvid, similar to other radiopharmaceuticals, contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Ensure safe handling to protect patients and health care workers from unintentional radiation exposure *[see Dosage and Administration (2.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In clinical studies, 496 patients were exposed to Amyvid. Amyvid caused no serious adverse reactions in the studies and the reported adverse reactions were predominantly mild to moderate in severity. The adverse reactions reported in more than one subject within the studies are shown in Table 2.

Table 2: Adverse Reactions Reported in Clinical Trials (N=496 patients)

Adverse Reactions	N (Percent of patients)
Headache	9 (1.8%)
Musculoskeletal pain	4 (0.8%)
Fatigue	3 (0.6%)
Nausea	3 (0.6%)
Anxiety	2 (0.4%)
Back pain	2 (0.4%)
Blood pressure increased	2 (0.4%)
Claustrophobia	2 (0.4%)
Feeling cold	2 (0.4%)
Insomnia	2 (0.4%)
Neck pain	2 (0.4%)

7 DRUG INTERACTIONS

Pharmacodynamic drug-drug interaction studies have not been performed in patients to establish the extent, if any, to which concomitant medications may alter Amyvid image results.

Within a clinical study of patients with a range of cognitive impairment, some patients with probable AD were receiving the following medications: donepezil, galantamine, memantine. Mean cortical Standardized Uptake Value (SUV) ratios did not differ between the patients taking or not taking these concomitant medications. In *in vitro* tests, none of the drugs tested, including the acetylcholinesterase inhibitors donepezil, galantamine, and tacrine, altered florbetapir F 18 binding to its target.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. It is not known whether Amyvid can affect reproductive capacity or cause fetal harm when administered to a pregnant woman. Animal reproduction studies have not been conducted with Amyvid. Amyvid should be administered to a pregnant woman only if clearly needed.

All radiopharmaceuticals, including Amyvid, have a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development and the magnitude of the radiopharmaceutical dose. Assess pregnancy status before administering Amyvid to a female of reproductive potential.

8.3 Nursing Mothers

It is not known whether Amyvid is excreted in human milk. Because many drugs are excreted into human milk and because of the potential for radiation exposure to nursing infants from Amyvid, avoid use of the drug in a breastfeeding mother or have the mother temporarily interrupt breastfeeding for 24 hours (>10 half-lives of radioactive decay for the F 18 isotope) after exposure to Amyvid. If breastfeeding is interrupted, the patient should pump and discard her breast milk and use alternate infant nutrition sources (e.g., stored breast milk or infant formula) for 24 hours after administration of the drug.

8.4 Pediatric Use

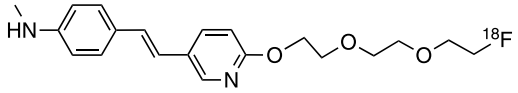
Amyvid is not indicated for use in pediatric patients.

8.5 Geriatric Use

Of 496 patients in completed clinical studies of Amyvid, 307 patients were ≥65 years old (203 patients were over 75 years of age). No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

11 DESCRIPTION

Amyvid contains florbetapir F 18, a molecular imaging agent that binds to β-amyloid aggregates, and is intended for use with PET imaging of the brain. Chemically, florbetapir F 18 is described as (E)-4-(2-(6-(2-(2-(2[^{18}F] fluoroethoxy)ethoxy)ethoxy)pyridine-3-yl)vinyl)-N-methylbenzamine. The molecular weight is 359 and the structural formula is:



Amyvid is a sterile, non-pyrogenic radioactive diagnostic agent for intravenous injection. The clear, colorless solution is supplied ready to use and each milliliter contains 0.1 to 19 micrograms of florbetapir and 500 - 1900 MBq (13.5 - 51 mCi) florbetapir F 18 at EOS, 4.5 mg sodium ascorbate USP and 0.1 mL dehydrated alcohol USP in 0.9% sodium chloride injection USP. The pH of the solution is between 5.5 and 7.5.

11.1 Physical Characteristics

Amyvid is radiolabeled with [^{18}F] fluorine (F 18) that decays by positron (β^+) emission to O 18 and has a half-life of 109.77 minutes. The principal photons useful for diagnostic imaging are the coincident pair of 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 3).

Table 3: Principal Radiation Produced from Decay of Fluorine 18

Radiation	Energy Level (keV)	Abundance (%)
Positron	249.8	96.9
Gamma	511	193.5

11.2 External Radiation

The point source air-kerma coefficient[a] for F-18 is 3.74E -17 Gy m^2/(Bq s); this coefficient was formerly defined as the specific gamma-ray constant of 5.7 R/hr/mCi at 1 cm. The first half-value thickness of lead (Pb) for F 18 gamma rays is approximately 6 mm[b]. The relative reduction of radiation emitted by F-18 that results from various thicknesses of lead shielding is shown in Table 4. The use of ~8 cm of Pb will decrease the radiation transmission (i.e., exposure) by a factor of about 10,000.

Table 4: Radiation Attenuation of 511 keV Gamma Rays by Lead Shielding

Shield Thickness cm of lead (Pb)	Coefficient of Attenuation
0.6	0.5
2	0.1
4	0.01
6	0.001
8	0.0001

[a] Eckerman KF and A Endo. MIRD: Radionuclide Data and Decay Schemes, 2nd Edition, 2008.

[b] Derived from data in NCRP Report No. 49. 1998, Appendix C

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Florbetapir F 18 binds to β-amyloid plaques and the F 18 isotope produces a positron signal that is detected by a PET scanner. In *in vitro* binding studies using postmortem human brain homogenates containing β-amyloid plaques, the dissociation constant (K_d) for florbetapir was 3.7 ± 0.3 nM. The binding of florbetapir F 18 to β-amyloid aggregates was demonstrated in postmortem human brain sections using autoradiographic methods, thioflavin S and traditional silver staining correlation studies as well as monoclonal antibody β-amyloid-specific correlation studies. Florbetapir binding to tau protein and a battery of neuroreceptors was not detected in *in vitro* studies.

12.2 Pharmacodynamics

Following intravenous injection, florbetapir F 18 diffuses across the human blood-brain barrier and produces a radioactivity signal detectable throughout the brain. Subsequently, cerebral perfusion decreases the brain florbetapir F 18 content, with differential retention of the drug in areas that contain β-amyloid aggregates compared to areas that lack the aggregates. The time-activity curves for florbetapir F 18 in the brain of subjects with positive scans show continual signal increases from time zero through 30 minutes post-administration, with stable values thereafter up to at least 90 minutes post-injection. Differences in the signal intensity between portions of the brain that specifically retain florbetapir F 18 and the portions of the brain with nonspecific retention of the drug forms the image interpretation methods *[see Dosage and Administration (2.5)]*.

Clinical studies evaluated the test-retest distribution of florbetapir F 18 within the brains of 21 subjects (11 with probable AD and 10 healthy volunteers) who underwent two injections (with PET scans), separated by a time period of 2 to 30 days. Images were shown to maintain signal distribution reproducibility when evaluated qualitatively (by a reader masked to image time points) as well as quantitatively using an automated assessment of SUV in pre-specified brain regions. A comparison of a 10-minute image acquisition time versus a 20-minute acquisition time showed no difference in the mean cortical to cerebellar SUV ratio results obtained.

12.3 Pharmacokinetics

Following the intravenous administration of 370 MBq (10 mCi) of florbetapir F 18 to healthy volunteers, the drug was distributed throughout the body with less than 5% of the injected F 18 radioactivity present in the blood by 20 minutes following administration, and less than 2% present by 45 minutes after administration. The residual F 18 in circulation during the 30-90 minute imaging window was principally in the form of polar F 18 metabolites. Whole body scanning following the intravenous injection showed accumulation of radioactivity in the liver within four minutes post-injection, followed by elimination of the radioactivity predominantly through the biliary/gastrointestinal tract with much lower radioactivity detected in the bladder. Essentially all radioactivity collected in the urine was present as polar metabolites of florbetapir F 18.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies to assess the carcinogenicity or reproductive toxicity potentials of Amyvid have not been conducted.

In an *in vitro* bacterial reverse mutation assay (Ames test), increases in the number of revertant colonies were observed in 2 of the 5 strains exposed to ^{19}F-AV-45, the non-radioactive form of florbetapir F 18. In a chromosomal aberration *in vitro* study with cultured human peripheral lymphocytes, ^{19}F-AV-45 did not increase the percentage of cells with structural aberrations with 3-hour exposure with or without activation; however, 22-hour exposure produced a statistically significant increase in structural aberrations at all tested concentrations. Potential *in vivo* genotoxicity of ^{19}F-AV-45 was evaluated in a mouse micronucleus study. In this assay, ^{19}F-AV-45 did not increase the number of micronucleated polychromatic erythrocytes at the highest achievable dose level, 372 µg/kg/day, when given twice daily for 3 consecutive days.

14 CLINICAL STUDIES

Amyvid was evaluated in three clinical studies that examined images from healthy adult subjects as well as subjects with a range of cognitive disorders, including some terminally ill patients who had agreed to participate in a postmortem brain donation program. All the studies were single arm studies in which subjects underwent an Amyvid injection and scan and then had images interpreted by multiple independent readers who were masked to all clinical information. Image interpretations used co-registration with CT scans when PET scans were performed on dual PET-CT scanners.

In Study One, a semi-quantitative Amyvid image interpretation method, which is not intended for clinical use, was used by three readers to interpret images from 152 terminally ill patients, of whom 35 underwent autopsy (29 included in primary analysis). The median patient age was 85 years (range 55 to 103 years) and 14 of the patients were female. Eighteen of the patients had dementia, 9 had no cognitive impairment and 2 had mild cognitive impairment (MCI). The main study outcome was a comparison of premortem Amyvid images to the findings from a postmortem brain examination (truth standard). The semi-quantitative measures consisted of a five-point whole brain Amyvid uptake image scoring outcome that was compared to a global score of the percentage of the whole brain that contained amyloid, as determined by immunohistochemical microscopy. The percentage of postmortem cortical amyloid burden ranged from 0 to 9% and correlated with the median Amyvid scores (Spearman's rho=0.78; $p<0.0001$, 95% CI, 0.58 to 0.89).

Studies Two and Three used a clinically-applicable binary image interpretation method (positive/negative) to evaluate images from a range of patients who had participated in earlier studies. The studies assessed performance characteristics (sensitivity and specificity) among subjects with a postmortem amyloid neuritic plaque density truth standard. Additionally, inter-reader and intra-reader image interpretation reproducibility was assessed among all the subjects, including subjects who lacked a postmortem truth standard. Before image interpretation, all readers underwent special training: Study Two used an in-person tutoring type of training and Study Three used an electronic media-based training method. Five trained readers interpreted images independently within each study. The brain neuritic plaque density in both studies was determined using an algorithm in which microscopic measures of highest plaque density within a brain region were averaged to produce a global brain estimate of neuritic plaque density. The global neuritic plaque density was categorized in the same manner as that for a region (Table 5),

where plaques were counted on slides with modified Bielschowsky silver stained tissue sections. For purposes of determining the agreement between the in-vivo Amyvid image results and the post-mortem whole brain amyloid neuritic plaque density, Amyvid results (negative/positive) were pre-specified to correspond with specific plaque density scores, based upon a modification of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria which use neuritic plaque counts as a necessary pathological feature of AD.

Table 5: Global and Regional Neuritic Plaque Density[a] Correlates to Amyvid Image Results

Neuritic Plaque Counts	CERAD Score	Amyvid Image Result
<1	none	Negative
1 - 5	sparse	
6 - 19	moderate	Positive
20+	frequent	

[a] J of Neuropathology and Experimental Neurology 1997; 56(10):1095.

Study Two examined images only from terminally ill patients who had premortem Amyvid scans and postmortem brain examinations to determine a truth standard. Among the 59 patients, 35 of whom were also in Study One, the median age was 83 years (range 47 to 103 years), half were females and most were Caucasian (93%). Twenty-nine patients had an AD clinical diagnosis, 13 had another type of dementing disorder, 12 had no history of cognitive impairment and 5 had MCI. The time interval between the Amyvid scan and death was less than one year for 46 patients and between one and two years for 13 patients. Among the subset of patients who died within one year of Amyvid scanning (a prespecified outcome), the sensitivity using the majority interpretation of the readers was 96% (95% CI: 80% to 100%) and specificity was 100% (95% CI: 78% to 100%). With the entire dataset of 59 patients, the sensitivity using the majority interpretation of the readers was 92% (95% CI: 78% to 98%) and specificity was 100% (95% CI: 80% to 100%). At autopsy, the global brain neuritic plaque density category (CERAD score, as in Table 5) was: frequent n=30; moderate n=9; sparse n=5; and none n=15. Tables 6 and 7 show the Amyvid performance characteristics among all the patients. Among the subset of patients who died within one year of Amyvid scanning (n=46; 28 positive and 18 negative based on histopathology) the median (and range) of correct read results, false negatives, and false positives were 44 (37 to 45), 1 (0 to 7), and 1 (0 to 2), respectively, for In-Person Training (Study Two); and were 43 (38 to 44), 3 (0 to 7), and 1 (0 to 2), respectively, for Electronic Media Training (Study Three).

Table 6: Amyvid Scan Results by Reader Training Method among Autopsied Patients (n = 59)

Test Performance		In-Person Training (Study Two)	Electronic Media Training (Study Three)
Sensitivity (%)	Median	92	82
	Range among the 5 readers	(69 – 95)	(69 – 92)
Specificity (%)	Median	95	95
	Range among the 5 readers	(90 – 100)	(90 – 95)

Table 7: Amyvid Correct and Erroneous Scan Results by Reader Training Method among Autopsied Patients

Read Result		In-Person Training (Study Two)					Electronic Media Training (Study Three)				
		Reader					Reader				
		1	2	3	4	5	6	7	8	9	10
All Scans with Autopsies (N=59[a])	Correct	55	56	53	56	45	49	54	46	53	51
	False Negative	3	2	5	3	12	8	3	12	5	7
	False Positive	1	1	1	0	2	2	2	1	1	1

[a] 39 positive and 20 negative based on histopathology

Study Three included images from subjects who did not have a truth standard (20 healthy volunteers, 52 patients with mild cognitive impairment, 20 patients with AD) as well as all 59 of the patients who underwent an autopsy (same patients as in Study Two) and provided a truth standard. Duplicate images of 33 patients were included within the total pool of images in order to assess intra-reader image reproducibility. Among the 151 subjects, the median age was 76 years (range 47 to 103), half were females and most were Caucasian (93.4%). Performance characteristics for patients with a truth standard are shown above (Tables 6 and 7). The major reproducibility results are shown in Table 8 for various groups of subjects. Inter-reader reproducibility analyses for all images showed an overall Fleiss' kappa statistic of 0.83 (95% CI: 0.78 to 0.88); the lower bound of the 95% CI exceeded the pre-specified success criterion (95% CI lower bound >0.58). Intra-reader reproducibility analyses showed that, between the two readings for each of the 33 patients with duplicate images, one of the five readers had complete

agreement for all 33 patients, two readers had discrepant reads for a single patient, one reader had discrepant reads for two patients and another reader had discrepant reads for three patients.

Table 8: Number of Positive Amyvid Scan Results within Study Three Subject Groups and Reproducibility of Scan Results Among Readers

Subject group by cognitive and truth standard (TS, autopsy) status	Positive Scans, n[a]	Kappa (95% CI)	Percent of Scans with Inter-reader Agreement		
			3 of 5 readers agree	4 of 5 readers agree	5 of 5 readers agree
All subjects with a TS, n=59	33	0.75 (0.67, 0.83)	14	10	76
All subjects without a TS, n=92	33	0.88 (0.82, 0.94)	2	11	87
AD, n=49 (29 with TS; 20 no TS)	38	0.67 (0.58, 0.76)	10	14	76
MCI, n=57 (5 with TS; 52 no TS)	17	0.91 (0.83, 0.99)	2	7	91
Cognitively normal without TS, n=20	4	0.83 (0.69, 0.97)	5	5	90
Cognitively normal with TS, n = 12	1	0.73 (0.55, 0.87)	0	8	92
Other (non-AD) dementia with TS, n = 13	7	0.52 (0.35, 0.69)	23	23	54

[a] Shown is the median number of scans interpreted as positive across the 5 readers for each subgroup of patients listed in the first column.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Amyvid is supplied in 10 mL, 30 mL, or 50 mL vials containing 10 mL, 10-30 mL, or 10-50 mL, respectively, of a clear, colorless solution at a strength of 500 - 1900 MBq/mL (13.5 - 51 mCi/mL) florbetapir F 18 at EOS. Each vial contains multiple doses and is enclosed in a shielded container to minimize external radiation exposure.

10 mL	NDC 0002-1200-10 (IC1200)
30 mL	NDC 0002-1200-30 (IC1200)
50 mL	NDC 0002-1200-50 (IC1200)

16.2 Storage and Handling

Store Amyvid at 25ºC (77°F); excursions permitted to 15ºC to 30ºC (59°F to 86°F) [see USP Controlled Room Temperature]. The product does not contain a preservative. Store Amyvid within the original container or equivalent radiation shielding. Amyvid must not be diluted.

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

17 PATIENT COUNSELING INFORMATION

- Instruct patients to inform their physician or healthcare provider if they are pregnant or breastfeeding.
- Inform patients who are breastfeeding to use alternate infant nutrition sources (e.g., stored breast milk or infant formula) for 24 hours (>10 half-lives of radioactive decay for the F 18 isotope) after administration of the drug or avoid use of the drug.

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Appendix B:

Summary of Clinical Trials Supporting Amyvid Labeled Indication

Clinical Studies Supporting Labeled Indication

The US Food and Drug Administration approved Amyvid in April 2012 for use as a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline.[116] A negative Amyvid scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations.

The following section provides brief summaries of the clinical studies supporting the FDA-approved label.

Study A07 (called "Study One" in the PI): Phase III Study of the Correlation Between Florbetapir F18 PET Imaging and Amyloid Pathology in the Brain[117]

ClinicalTrials.gov Identifier: NCT00857415

Objective: To test the relationship between measurements of amyloid burden using florbetapir F 18 positron emission tomography (Amyvid PET) imaging and true levels of amyloid burden determined at autopsy.

Methods: In this prospective clinical evaluation, Amyvid PET brain images of 35 patients from hospice, long-term care, and community health care facilities near the end of their lives were compared to histopathological measures of brain beta-amyloid using immunohistochemistry at autopsy as the reference standard. Six patients were analyzed separately to establish the protocol and 29 patients made up the primary analysis/autopsy cohort. Three independent imaging physicians evaluated the Amyvid PET scans in randomized blinded fashion. Neuropathology analyses were independently performed and were blinded to any clinical information, image data or reading results. The study's primary endpoint was to determine if there was a statistically significant correlation between the semi-quantitative visual rating of amyloid burden of the Amyvid PET scan and the cortical amyloid burden at autopsy.

Results: Among the 29 individuals in the primary analysis cohort, 31% were not considered to be cognitively impaired by the enrolling physician, 7% were considered mildly impaired but without dementia, 45% had a clinical diagnosis of AD, and 17% had a clinical diagnosis of a non-AD dementia. Both visual interpretation of the Amyvid PET images and mean quantitative estimates of cortical uptake were correlated with presence and quantity of beta-amyloid pathology at autopsy with statistical significance ($p < .001$). Qualitative visual interpretation of

the Amyvid PET images derived from the median reader score yielded a sensitivity of 93% (95% CI, 68%-100%) and a specificity of 100% (95% CI, 76.8%-100%). Overall, the qualitative evaluation using the median reader score of Amyvid PET images and postmortem results for beta-amyloid agreed in 96% of the 29 individuals in the primary analysis cohort.

Conclusion: This was the first prospective, multicenter trial that demonstrated the possibility to both directly identify and quantify the presence of beta-amyloid aggregates using Amyvid PET in living patients.

Study A08: Evaluation of Physician Training Methods to Read Florbetapir-PET Scans[118]

ClinicalTrials.gov Identifier: NCT01565369

Objective: To evaluate a training program developed to educate physicians in the binary interpretation of Amyvid PET images.

Methods: This study evaluated a reader training method developed for routine clinical practice. Nine private practice nuclear medicine physicians with no prior training in reading Amyvid PET scans were given in-person training on how to perform a binary ("Aβ+" or "Aβ-") beta-amyloid interpretation. Reader proficiency in interpretation was then tested using images obtained from the 35 subjects that came to autopsy in the Phase III study A07. Sensitivity and specificity were evaluated using the CERAD categorization of amyloid pathology as the reference (or "truth") standard (Table 3). The inter-reader reproducibility of the binary reading methodology was evaluated using Fleiss' kappa statistic.

Table 3. CERAD Scoring of Neuritic Plaque Density

Neuritic Plaque Counts	CERAD Score	Truth Standard
<1	none	Negative
1-5	sparse	
6-19	moderate	Positive
20+	frequent	

Adapted from J Neuropathology 1997; 56(10):1095

Results: The median sensitivity, specificity, and accuracy across the 9 individual reviewers relative to the pathology reference standard were 100% (84.2%-100%), 93.8% (68.8%-100%), and 94.3% (85.7%-97.1%), respectively. Eight of the 9 readers achieved greater than 90% accuracy relative to the reference standard. Overall, 96.2% of individual reads agreed with the majority read. The overall Fleiss' kappa was 0.85 ($p < 0.0001$) indicating excellent reader-to-reader agreement.

Conclusion: The proposed reader training methodology is effective in teaching readers how to accurately and reliably interpret Amyvid PET scans using a prospectively-defined binary rating scale.

Study A16 ("Study Two" in the PI): Autopsy Follow-up of Subjects Previously Imaged With Florbetapir F 18 (18F-AV-45) PET in Trial 18F-AV-45-A07

ClinicalTrials.gov Identifier: NCT01447719

Objective: To test the relationship between measurements of amyloid burden using Amyvid PET imaging and true levels of amyloid burden determined at autopsy.

Methods: The study was designed to test the sensitivity and specificity of an independent blinded visual read assessment of the Amyvid PET scan (Aβ+ or Aβ-) versus the final blinded neuropathological diagnosis made at autopsy, as well as the correlation between the blinded semi-quantitative rating of brain amyloid using Amyvid PET imaging and beta-amyloid levels determined at autopsy. Visual qualitative reads were carried out by five readers who were trained to use the binary read methodology intended for routine clinical use. Subjects who were previously enrolled in the A07 study and imaged with Amyvid were followed to autopsy for an additional 12 months beyond the last completed autopsy. Subjects with autopsies obtained under the A07 and A16 protocol were pooled for analysis. Primary outcome measures were sensitivity and specificity of Amyvid PET to detect moderate to frequent amyloid plaques using majority reading among 5 readers, and correlation of Amyvid PET and amyloid burden assessed post-mortem by quantitative immunohistochemistry.

Results: At the end of the A16 study, 59 subjects had completed brain autopsy neuropathology procedures comprising the primary analysis population. Clinical diagnoses in the primary analysis population included 29 subjects with AD, 13 with another type of dementing disorder, 12 with no history of cognitive impairment or dementia, and 5 with mild cognitive impairment (MCI). The sensitivity, specificity and accuracy of qualitative image read by majority rating among the five readers were the following:

- Sensitivity = 92% (95% CI: 78% to 98%)
- Specificity = 100% (95% CI: 80% to 100%)
- Accuracy = 95% (95% CI: 85% to 99%).

Correlation analyses between the median blinded visual read of the florbetapir PET scan and beta-amyloid density assessed by quantitative immunohistochemistry for each region revealed a statistically significant Spearman's ρ above 0.65 for each region of the brain (each $p<0.0001$).

Conclusions: The sensitivity and specificity of the majority visual read score for detecting probable/definite AD pathology at autopsy exceeded study objectives (target value of 80%). Additionally, Fleiss' kappa statistic showed a high degree of agreement among the five blinded readers for the qualitative analysis. The range and distribution of beta-amyloid neuritic plaque

histopathology results obtained in this study population are similar to that in neuropathology literature reports of subjects having clinical diagnoses of MCI or AD and, therefore, appear to be representative of the range and distribution of beta-amyloid plaque levels expected in a general population of cognitively impaired individuals.

Study PT01 (Study Three in the PI): Evaluation of Web-based Training to Educate Physicians in the Methods of Interpreting Florbetapir-PET Scans

ClinicalTrials.gov Identifier: NCT01550549

Objective: To validate a web-based training program that would be used to educate nuclear medicine and radiology physicians in the methods of interpreting Amyvid PET scans in a standard clinical setting.

Methods: Five nuclear medicine physicians completed an automated training program using the previously developed binary read methodology of interpreting Amyvid PET scans originally implemented in an in-person format for studies A08 and A16. Images from 92 subjects from study A05 (NCT00702143) and 59 autopsy subjects from study A07 and its extension A16 (a total of 151 subjects) with repeat readings of 33 randomly selected images (184 images in total) were used to test the training in this study. Subjects from study A05 were originally enrolled with one of the following three clinical diagnostic categories: 1) cognitively normal, 2) MCI, and 3) probable AD. In Study PT01, readers rated each case as either positive or negative for significant tracer accumulation in cortical gray matter. The study's primary aim was to evaluate the inter-reader reliability of Amyvid PET scan interpretation using Fleiss' kappa statistic. The secondary aim was to evaluate diagnostic performance (i.e., sensitivity and specificity) of reader interpretation.

Results: Primary analysis results showed a Fleiss' kappa statistic of 0.81 (95%CI: 0.75-0.87) for inter-reader reliability. Median sensitivity and specificity across the 5 individual readers relative to the pathology reference standard were 82% (69%-92%) and 95% (90%-95%), respectively. The sensitivity and specificity of the majority interpretation of the florbetapir PET scans for detecting moderate to frequent plaques was 92% (36/39; 95% CI 78-98%) and 100% (20/20; 95% CI 80-100%), respectively, for cases that came to autopsy within two years, and 96% (27/28; 95% CI 85-100%) and 100% (18/18; 95% CI 80-100%), respectively, for cases that came to autopsy within one year.

Conclusion: This study validates the previously developed binary read methodology as well as the web-based training materials designed to educate physicians' interpretation of Amyvid PET scans in a clinical practice environment. Study results demonstrated good inter-reader reproducibility and accuracy.

Appendix Table 1. Clinical evidence summary

Study ID	Design	Eligibility Criteria	N	Objective(s)	Results	Publication
A07	Blinded, multi-center	Autopsy cohort: • Male or female subjects, ≥18 years of age • Projected life expectancy of ≤6 months Specificity Cohort: • Cognitively and neurologically healthy male and female subjects, 18 to 40 years of age • No known risk factors for AD	226	To test the relationship between measurements of amyloid burden using florbetapir F 18 positron emission tomography (florbetapir PET) imaging and true levels of amyloid burden determined at autopsy.	• Statistically significant positive correlations were observed between florbetapir PET (both blinded visual reader assessment and computerized SUVR measurement) and histopathologic measurements of beta-amyloid (n=29). • The sensitivity and specificity of the florbetapir-PET qualitative read derived from the median reader score was 93% and 100%, respectively; overall accuracy was 96%	Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA 2011;305:275-83.
A08	n/a	Images from subjects who received florbetapir PET scans and subsequently came to autopsy in study A07 were utilized to test the training in this study.	35	To evaluate a training program developed to educate physicians in the binary interpretation of florbetapir PET images	• The median sensitivity, specificity, and accuracy across the 9 individual reviewers relative to the pathology reference standard were 100%, 93.8% and 94.3%, respectively. • 8 of the 9 readers achieved greater than 90% accuracy relative to the reference standard. • The overall Fleiss' kappa was 0.85 ($p < 0.0001$) when comparing multiple individual readers, indicating good reader-to-reader agreement.	n/a

Study ID	Design	Eligibility Criteria	N	Objective(s)	Results	Publication
A13	n/a	• Clinical data and florbetapir imaging results from subjects who participated in an early study, A05. • Cohort: an equal number of subjects with clinical diagnosis of AD and MCI, with equal numbers of Aβ positive and Aβ negative florbetapir PET scans for each of the two groups.	44	To determine if information from a florbetapir PET scan could change an expert clinician's diagnosis.	• The expert clinician's initial diagnosis (blinded to the diagnosis given to the subject by the original enrolling physician) indicated either cognitive impairment of indeterminate origin or was inconsistent with florbetapir PET scan results (e.g., dementia due to AD in a patient with an amyloid negative PET scan) in 59% of the 44 cases (range 50-66%). • After florbetapir PET scan results were unblinded, these experts changed their diagnosis in 85% (range 66-100%) of the cases with indeterminate origin or inconsistent with PET scan results. • This represented a significant shift in diagnostic thinking ($p < 0.001$, 95% CI 80-100%).	n/a
A16	Blinded, multi-center	Previously enrolled in the autopsy cohort of study 18F-AV-45-A07	59	To test the relationship between measurements of brain beta-amyloid using florbetapir F 18 positron emission tomography (PET) imaging and beta-amyloid as measured by histopathological assessment	• 29 subjects had a clinical diagnosis of AD, 13 had another clinically-diagnosed dementing disorder, 5 had a clinical diagnosis of mild cognitive impairment (MCI), and 12 had no history of cognitive impairment or dementia • The majority visual read score for detecting probable/definite AD pathology at autopsy had a sensitivity of 92% (95% CI: 78% to 98%), and a specificity of 100% (95% CI: 80% to 100%) with an overall accuracy of 95% (95% CI: 85% to 99%) • The median sensitivity was 92% (range: 69% to 95%) and median specificity 95% (range: 90% to 100%)	Clark CM, Pontecorvo MJ, Beach TG, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: a prospective cohort study. The Lancet Neurology, Early Online Publication, 28 June 2012. doi:10.1016/S1474-4422(12)70142-4.

Study ID	Design	Eligibility Criteria	N	Objective(s)	Results	Publication
PT01	n/a	Images from subjects in studies A05, A07 and its extension, A16, were utilized to assess the training in this study.	151	To validate a web-based training program that would be used to educate nuclear medicine and radiology physicians in the methods of interpreting florbetapir F 18 positron emission tomography (PET) scans in a standard clinical setting	• The Fleiss' kappa was 0.81 (95% CI: 0.75-0.87) for inter-reader agreement analysis • The median sensitivity and specificity among the five individual reviewers relative to the pathology reference standard were 82% and 95%, respectively.	n/a

Appendix C:

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