CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202008Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 26, 2012
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	202008
Applicant Name	Avid Radiopharmaceuticals, Inc.
Date of Submission	September 17, 2010 for original submission; CR letter issued on March 17, 2012; Resubmission on October 7, 2011
PDUFA Goal Date	April 7, 2012
Proprietary Name / Established (USAN) Name	Amyvid™ Injection Florbetapir F18
Dosage Forms / Strength	Amyvid is to be supplied in 10 mL vials (b) (4) ; the recommended dose is 370 MBq (10 mCi) administered intravenously to adults.
Proposed Indication(s)	The indication ultimately proposed for marketing is: 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 (b) (4). 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 (b) (4) amyloid neuritic plaque in the brain; neuropathological examination has shown this amount of amyloid neuritic plaque in patients with AD, patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations (b) (4) (b) (4) <u>Limitation of Use:</u> Safety and effectiveness of Amyvid have not been

	established for the following: • As an AD diagnostic test; • For predicting development of dementia; • For monitoring patient responses to AD therapies.
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Qi Feng, MD, PhD & Lucie Yang, MD, PhD (Acting TL)
Statistical Review	Lan Huang, PhD & Jyoti Zalkikar, PhD
Pharmacology Toxicology Review	Sunday Awe, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Ravindra Kasliwal, PhD
Microbiology Review	Stephen Langille, PhD
Clinical Pharmacology Review	Christy John, PhD & Y. Moon Choi, PhD (TL for original cycle) Gene Williams, PhD (TL) for resubmission cycle
DDMAC	James Dvorsky for the resubmission cycle
DSI	Anthony Orencia, MD for original cycle John Lee, MD for resubmission cycle
CDTL Review	Lucie Yang, MD, PhD
OSE/DMEPA	Kevin Wright, PharmD (resubmission cycle) Denise Baugh, PharmD & Todd Bridges, PharmD (TL)
OSE/DRISK	Suzanne Berkman-Robottom/meeting for 2/24/11 during the original cycle;
Pediatric and Maternal Health	Tammie Howard, RN & Karen Feibus, MD (TL); Jeanine Best for resubmission cycle
Project Manager	Sharon Thomas, MS
Neurology Consultatnts	Nicholas Kozauer, MD, Rajit Manni, MD & Russel Katz, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
TL = Team Leader
CMC = chemistry, manufacturing and controls

Unless otherwise noted above, the team members were the same for the original review cycle and the resubmission review cycle.

1. Introduction:

This document summarizes my concurrence upon the plan to approve this application. At the present time, we are finalizing labeling so the ultimate labeling indication statement may somewhat differ from the one listed above. We are in the process of also finalizing post-marketing commitments, so these items are not described in detail here.

In September, 2010 Avid Radiopharmaceuticals submitted a New Drug Application (NDA) to support the marketing of Amyvid™, a radiopharmaceutical imaging agent (F18 positron emission tomography drug). The review cycle concluded with a Complete Response (CR) letter that cited deficiencies in three main areas: 1) Clinical (need for standardized, reproducible image interpretation methods) 2) Manufacturing (need for revision of container labeling) and 3) Facility inspection issues.

The original review observations were discussed at a January 20, 2011 meeting of the Peripheral and Central Nervous System Advisory Committee. The committee voted (13 to 3) to recommend against approval of Amyvid during the original review cycle due deficiencies related to image interpretation methods (insufficient development of reader training methods that allow reproducible and accurate image interpretation). The committee did vote (16 to 0) in support of the drug in response to the question, "If there were implementation of a training program that demonstrated accurate diagnosis within the autopsy/standard population and a demonstration of reader consistency in the population of intended application such as exemplified by A05, would the available data support the approval of Amyvid?"

The sponsor submitted a response to the CR letter of March, 2011. The main feature within the response was the submission of Study PT01 results that verified Amyvid scans can be accurately and reproducibly interpreted by conventional imaging professionals.

The review team has completed draft labeling and recommends approval. Amyvid scan reproducibility/reliability meets or exceeds that associated with other drug imaging tests. The draft Amyvid labeling appropriately describes the benefits, risks and limitations associated with the drug and scan.

2. Background:

The active moiety within Amyvid, florbetapir, is a form of a dye that bind to aggregated (fibrillar amyloid) in a manner that may be similar to the binding of other dyes (e.g., silver stains or Congo Red) to aggregated amyloid. The biochemistry of amyloid is relatively complex and evolving. Currently, amyloid is generally recognized as a derivative of a neuronal cell transmembrane protein called Amyloid Precursor Protein (APP). Cleavage of portions of the APP liberates amyloid proteins that are soluble but that may aggregate to form extracellular insoluble complexes (aggregated amyloid, predominantly a beta-sheet conformation). The active moiety within Amyvid (florbetapir) has been shown to selectively bind to aggregated amyloid within brain amyloid plaques; amyloid plaques are variously known as neuritic plaques

(histopathological signs of neuronal destruction) and senile plaques. The presence of aggregated amyloid within neuritic plaques is one of the defining hallmarks of Alzheimer's Disease; absence of these plaques precludes a neuropathologic diagnosis of Alzheimer's Disease. Neuritic amyloid plaques are observed in multiple conditions, including normal aging; hence, the presence of these plaques alone is not sufficient to establish a diagnosis of Alzheimer's Disease.

The development of Amyvid followed a paradigm that was articulated at an advisory committee held in 2008 (October 23, 2008). This advisory committee discussed the types of studies necessary for an applicant to develop a drug for the imaging of brain amyloid. The most notable conclusion from this committee discussion was that histopathology (e.g., autopsy) tissue must serve as the "truth standard" for a drug that images amyloid and that the clinical detection of aggregated amyloid with an imaging agent could have clinical usefulness (apart from any specific diagnostic capability of the image). The committee noted that a "negative" amyloid image would be especially useful to lessen the diagnostic likelihood that a patient with cognitive impairment (suspected of Alzheimer's Disease, AD) had AD.

Subsequent to the 2008 advisory committee, Avid Radiopharmaceuticals performed a single phase 3 study that involved the Amyvid imaging of a group of "end of life" patients. Once these patients died (n = 35 in the original review cycle/59 in the resubmission cycle), an autopsy was performed to detect amyloid within the brain. The main clinical efficacy data are obtained form 3 studies which are referred to in labeling as Studies One through Three (in reviews, the following terms were applied, based upon the study protocol numbers: Study One = Study A07; Study Two = Study A16; Study Three = Study PT01).

Based upon three major lines of evidence, we conclude Amyvid measures brain amyloid plaque in a manner that allows its use in accordance with the labeling indication cited above. Specifically:

1) *In vitro* studies of florbetapir binding:

In vitro studies of florbetapir binding to the gray matter brain homogenates of humans with AD showed intense but reversible binding of the agent to brain homogenates. Autoradiography of healthy and AD brains showed florbeta;pir binding to sections of the brain that contained amyloid plaques with no specific labeling in healthy brains. Similar results were obtained in studies of transgenic mice that over-expressed amyloid.[1]

2) Study One demonstrated solid correlation of semi-quantitative scan results with quantitative IHC results in the brains of 29 subjects who had autopsy.

3) Study Three showed acceptable performance characteristics among 59 subjects who had autopsies. Study Two and Three showed reproducibility assessments (inter-reader and intra-reader) that were acceptable (either similar to or exceeding that of currently

[1] J Nucl Med 2009; 50:1887-1894.

used imaging tests). Studies Two and Three consisted of pooled images from a subjects who had participated in earlier Amyvid drug development studies.

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed mainly by Dr. Ravindra Kasliwal during the original and resubmission review cycle. The original and resubmission cycle microbiology review was performed by Dr. Stephen Lanignelle. The reviewers verified acceptable manufacturing procedure during the resubmission cycle and recommended approval. Facility inspections are complete and document sufficiency for NDA approval.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the Dr. Sunday Awe, the pharmacology/toxicology reviewer who, during the original review cycle, noted that there are no outstanding pharm/tox issues that preclude approval, beyond the development of acceptable labeling. The main observations from the original review cycle were:

In vitro and *ex vivo* studies verified that florbetapir binds to aggregated amyloid within the human brain. Safety toxicology studies verified no adverse effects in rats at up to 21X the maximum human dose; and in beagles at up to 84X the maximum human dose. Some genotoxicity potential was identified by *in vitro* studies (Ames/peripheral lymphocyte) but these observations were not supported by *in vivo* findings (negative mouse micronucleus assay) such that the drug was assessed as having no meaningful genotoxicity risk. A waiver was granted for repro-tox studies.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer during the original review cycle that there are no outstanding clinical pharmacology issues that precluded approval. The review team noted that Amyvid is rapidly cleared from the blood (within minutes) and is metabolized in the liver; excretion is predominantly through the biliary system/intestine.

During the resubmission cycle the clinical pharmacology team highlighted the apparent nonspecific brain white matter binding of florbetapir in Amyvid scans.

During my examination of the data, I found that the sponsor (and others, in publications, see subsequent Villemagne reference) have attributed the apparent nonspecific brain white matter florbetapir binding (as seen in Amyvid scans) to the lower blood flow through the brain white matter, compared to the gray matter. While this "nonspecific" binding has been regarded by some complicating Amyvid scan interpretations, the sponsor has developed a reading method (as assessed in Study Two and Three) that minimizes complications in image interpretation due to the nonspecific white matter florbetapir binding. Specifically, the labeling describes the unique features of the image interpretation (identification of brain gray-white contrast hallmark findings between

"negative" and "positive"). These features were rigorously studied by 10 independent Amyvid scan readers (5 who were trained using an in-person tutorial and 5 who were trained using an electronic media-based tutorial). Comparisons of inter-reader reproducibility using a Fleiss kappa measurement showed success upon the desired outcome; specifically the kappa statistic was 0.83 (95% CI of 0.78 to 0.88). This extent of reproducibility is similar to or exceeds that cited for other nuclear medicine tests.

For example, one publication has bone scintigraphy interpretations producing an average kappa value of 0.48 (range 0.16-0.82)[2] and another cites somatostatin receptor scintigraphy interpretations as producing linear weighted Cohen kappa value of 0.59 (95% CI: 0.32 – 0.87).[3] These publications do not give full details of their statistical tests but they do discuss the common (and clinically accepted) limited extent of reproducibility of commonly used and clinically important nuclear medicine tests. These limitations are not unique to nuclear medicine tests; for example, a kappa value of 0.73 (95% CI: 0.69 – 0.77) has been cited in magnetic resonance imaging assessment of spinal stenosis.[4]

6. Clinical Microbiology:

The original cycle microbiology reviewer recommended approval and I concur with his findings. No post-marketing studies were proposed.

7. Clinical/Statistical-Efficacy:

Dr. Qi Feng provided the main clinical review and Dr. Lan Huang and Dr. Jyoti Zalikar provided the main statistical review. Dr. Lucie Yang provided a secondary clinical review. The statistical review was complicated by a medical emergency and Dr. Zalkikar's secondary review incorporates the primary reviewer's observations, as they were articulated at the mid-cycle meeting. The reviewer's original cycle reviews disclosed unacceptable limitations in image interpretation (as discussed at the 2011 advisory committee). The reviewers' resubmission findings supportive approval because the image reading methodology had been developed and verified as producing acceptable reproducibility.

The main clinical and statistical data are described in the drug labeling. I will summarize the original cycle findings and restate the labeling text on clinical studies.

Original cycle findings:

[2] Sadik, et. al. Quality of planar whole-body bone scan interpretations—a nationwide survey. Eur J Nucl Med Mol 2008; 35(8) 1464-72.
[3] Apostolova, et. al. SPECT/CT stabilizes the interpretation of somatostatin receptor scintigraphy findings: a retrospective analysis of inter-rater agreement. Ann Nucl Med 2010; 24:477-483.
[4] Lurie, et. al., Reliability of readings of magnetic resonance imaging features of lumbar spinal stensosi. Spine 2008; 33 (14) 1605.10.

The single Phase 3 study (A07) was titled "A Phase III study of the correlation between florbetapir F 18 (^{18}F-AV-45) positron emission tomography imaging and amyloid pathology." Study A07 enrolled two different populations to address two primary endpoints (one related to an "autopsy cohort" and the other related to a "specificity cohort"—two different populations).

Study population: The "autopsy" cohort comprised of adults with a projected life expectancy of ≤6 months. There were 152 subjects in the autopsy cohort imaged and 29 subjects were included in the primary efficacy analysis for correlation with histopathology (autopsied patients). The "young, cognitively intact cohort" (YCI) comprised adults equal to or younger than 40 years without risk factors for Alzheimer's Disease (AD). The sponsor referred to this cohort as the "specificity cohort." Of the 74 subjects in the YCI cohort imaged, only the 47 subjects who were negative for the genetic risk factor ApoE ε4 were included in the "specificity" primary endpoint analysis.

PET image interpretation method: Importantly, the PET image interpretation method for the two endpoints were different. For the autopsy cohort, PET image interpretation for amyloid burden in the cortical gray matter throughout the brain was on a 5-point scale semi-quantitative visual rating of amyloid burden (0-4, with 0 = none, 4 = high). For the YCI cohort, a binary scale was used to visually characterize amyloid status in the cortical gray matter in the entire brain as positive or negative. The YCI cohort PET images (presumably negative for amyloid) were randomized with PET images from the first 40 autopsy cohort subjects with a median (of 3 readers for the autopsy cohort) score suggestive of positive amyloid burden (2 or greater on the 5-point scale) to reduce bias.

Reference standard: Histopathology was used to unequivocally determine amyloid burden for the autopsy cohort. Patients who expired within one year of PET imaging underwent autopsy. Quantitative histochemistry (IHC) was used to determine the average percent area occupied by amyloid averaged across six brain regions (representing a cross-section of major cortical areas). In contrast, for the YCI cohort, the reference standard was a negative amyloid status assumed based on age, history, intact memory and cognition, and absence of risk factors for AD.

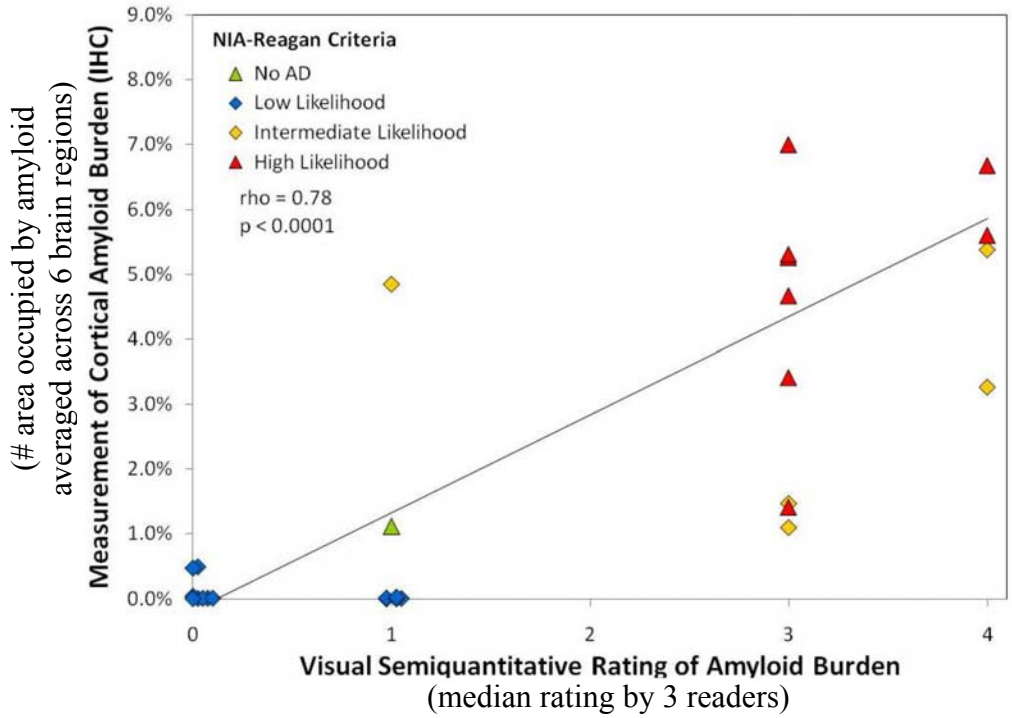
Primary efficacy endpoint: For the autopsy cohort, the primary efficacy endpoint was correlation between (a) amyloid burden in the brain, at the patient level, using a semi-quantitative visual rating scale (0-4) for Amyvid PET images (median of 3 independent readers) and (b) the cortical amyloid burden by pathology using quantitative IHC. Achieving success required a statistically significant correlation (Spearman's $\rho>0$, $p\leq0.05$). For the YCI cohort, the primary efficacy endpoint was detection / exclusion of amyloid, at the patient level (majority of 3 readers). Success was defined as "specificity" ≥90% (95% CI: 80-98%). "Specificity" is in quotes because the standard of truth is presumed rather than demonstrated.

All subjects enrolled into A07 were dosed with 10 mCi of Amyvid 50 minutes prior to PET imaging. For each endpoint, images were read by a different set of three readers blinded to clinical information. When computed tomography (CT) images of the head

were obtained for attenuation correction, readers of PET images had access to these CT images.

Results: Review of efficacy data for the 29 subjects in the autopsy cohort who died (and whose images were not used to refine study methods, n=6) showed that a statistically significant correlation was achieved, with Spearman's ρ=0.78, p<0.0001. Thus, the primary endpoint was met for the autopsy cohort.

Autopsy Cohort Primary Efficacy Result.



For the YCI cohort, "specificity" was 100% for the 47 subjects who did not have the genetic risk factor for AD, ApoE ε4. Although the primary endpoint was met, there are important limitations. First, the negative amyloid status used as the reference standard was presumed rather than confirmed by pathology. Second, although the sponsor made an effort to minimize bias by randomizing PET images that were presumably positive for amyloid (from the autopsy cohort) into the image pool of the 47 YCI subjects, it is possible that reader access to structural information on CT images could have biased the interpretation of amyloid status in favor of amyloid absence for the young, cognitively healthy individuals: not only is the enrolled population not in the population of intended use, but the brains of these younger individuals (mean age 26 years) most likely show much less (if any) cortical atrophy on CT than those of the 40 autopsy cohort individuals whose PET images were added to the image pool (mean age 79 years).

Conclusions: Even though the phase 3 study met its primary endpoints; the image interpretation methods used in this study are not directly clinically applicable.

Development of clinically-applicable reader training material and verification of the reliability of Amyvid image interpretation is the main outstanding deficiency.

Supportive Studies: Background (phase 1 and 2) clinical studies were useful in showing the test-retest fidelity of Amyvid image acquisition and image reinterpretation when performed by a single reader using a study-specific method. Additionally, the phase 2 study referred to as "A05" included a broad range of older subjects (some normal, some with mild cognitive impairment and some with Alzheimer's disease). Image interpretation in Study A05 used a relatively intense reader training program that is not proposed for clinical use; reinterpretation of Study A05 images using the clinically-applicable reader methods will importantly help assess the reproducibility of Amyvid imaging, as it is to be used clinically.

Resubmission cycle findings:

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 7% 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 correlating Amyvid image results to the whole brain amyloid neuritic plaque density, Amyvid results (negative/positive) were pre-specified to correlate with specific plaque density scores, based upon a modification of criteria developed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).

Table 5: Global and Regional Neuritic Plaque Density* 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	

* 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 median sensitivity among the readers was 96% (95% CI: 80% to 100%) and specificity was 100% (95% CI: 78% 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.

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 (n = 59*)

Read Result	In-Person Training (Study Two)					Electronic Media Training (Study Three)				
	Reader					Reader				
	1	2	3	4	5	6	7	8	9	10
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

*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, only 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 (%)*	Kappa (95% CI)	Percent agreement (%)**		
			3 agree	4 agree	5 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	8	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

* Shown is the median number of scans interpreted as positive across the 5 readers for each subgroup of patients listed in the first column
** Percent agreement among the 5 readers of each subject's images

Other Notes:

During the review cycle the FDA received a letter from Public Citizen, that noted, *"As you are aware, in our letter to you dated February 21, 2011, and in our recently published letter to the editor of the Journal of the American Medical Association, we urged the Food and Drug Administration (FDA) not to approve Avid Pharmaceuticals' New Drug Application (NDA), # 202-008, for florbetapir F18 injection (Amyvid) because of the significant inter-reader variability that was seen in the single phase 3 clinical trial evaluating the performance of florbetapir positron emission tomography (PET) imaging. Given such inter-reader variability, such PET scans would have little clinical utility in the evaluation of patients presenting with cognitive deficits or early dementia and suspected of having Alzheimer's disease (AD).*

In an editorial just published on-line in the European Journal of Nuclear Medicine and Molecular Imaging (copy enclosed), experts in the field of PET neuroimaging have identified even more fundamental problems with the results of studies cited by Avid Pharmaceuticals in its NDA that undermine any support for the following proposed indication for florbetapir-PET scans:

Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for [PET] imaging of beta-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of beta-amyloid in the brain."

This letter identified several points (mainly from the publication[5]) which were addressed during the review cycle. Of note, the authors of the letter to the FDA did not cite or

[5] Moghbel, et. al., Amyloid-beta imaging with PET in Alzheimer's disease: is it feasible with current radiotracers and technologies? Eur J Nucl Med Mol Imaging 2012; 39:202-208.

describe the companion publication[6] that addressed most of the points. The following reiterate some of the review observations as they apply to the main points of the letter to the FDA:

1. Reproducibility of image interpretation: The second cycle review was predominantly focused upon the review of the sponsor's newly developed image interpretation methods and the verification of the reproducibility of the image interpretation process. These data thoroughly address the reproducibility concern.

2. The letter expressed concern about the distribution of beta-amyloid deposits in the brain as shown by florbetapir scans in AD patients when compared to that seen with histopathological and immunohistochemical studies. This concern has been thoroughly addressed in publications (reference 6 details how the beta-amyloid imaging agent distribution in the brain actually does parallel histopathological brain amyloid deposition) and data submitted to the NDA. A sample of the NDA data was described in a publication[7] that specifically examined florbetapir binding in frontal cortex brain.

3. The letter expressed concern about nonspecific white matter uptake of the Amyvid F18 radioisope in the brain. This observation is correct in that there is retention of the F18 signal in human brain white matter, perhaps due to lesser blood flow through the white matter in comparison to the gray matter. However the concern has been remedied by the sponsor through the development of specific image interpretation methods that focus upon features of gray-white istope uptake. These features are highlighted within the training methods which are largely duplicated within labeling.

Overall, the Public Citizen letter highlighted some of the considerations the sponsor addressed within the NDA resubmission.

8. Safety:

The most notable safety findings pertain to the radiation risks implicit for radiopharmaceuticals as well as the risks associated with unreliable image interpretation. The radiation risks for Amyvid are similar to that of currently marketed radiopharmaceuticals. The risks associated with unreliable image interpretaition is arguably the most important safety risk since an unreliable image interpretation may prompt the performance of additional clinical tests that cause harm to patients. The sponsor has developed image interpretations methods that were reliable/reproducible when evaluated in clinical study. At the time of this review development, a post-marketing commitment is under development for a study that will help to assess the fidelity of image interpretation at clinical sites to image interpretation at a central facility with very experienced readers.

[6] Villemagne, et. al., Abeta Imaging: feasible, pertinent and vital to progress in Alzheimer's disease. Eur J Nucl Med Mol Imaging 2012; 39: 209-219.
[7] Choi, et. al. Correlation of amyloid PET ligand florbetapir F18 binding with Abeta aggregation and neuritic plaque deposition in postmortem brain tissue. Alzheimer Dis Assoc Disord 2012; 26:8-16.

Post-marketing Requirements (PMR): none

Post-marketing Commitments (PMC):
We are currently working out a plan for a couple of PMC that pertain to 1) assessment of the reliability of site Amyvid scan interpretations, as they are performed in clinical practice and 2) the ability to use quantitative imaging parameters to interpret scans. Details are under discussion at the current time.

9. Advisory Committee Meeting:

This application was not reviewed at an Advisory Committee during the resubmission cycle. The original application was presented to the Peripheral and Central Nervous System Advisory Committee on January 20, 2011. The committee voted (13 to 3) to recommend against approval of Amyvid during the original cycle; deficiencies related to image interpretation methods, as noted above. The committee emphasized the acceptability of the data if a sufficient reader training program could be developed.

10. Pediatrics:

In an email document from Mr. George Greeley, the team was informed that the PeRC PREA Subcommittee reviewed AMYViD on November 3, 2010 and agreed to grant a full waiver for PREA-related studies; the committee noted that the applicable disease/condition does not exist in children.

11. Other Relevant Regulatory Issues:

Inspection of the phase 3 clinical data (3 sites) detected no deficiencies during the original review cycle. During the resubmission cycle, the contract research organization (b) (4) which was responsible for the conduct of Study PT01 (Study Three) was inspected. DSI detected no deficiencies within the (b) (4) inspection.

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/s/

RAFEL D RIEVES
03/28/2012