CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202008Orig1s000

MEDICAL REVIEW(S)

CLINICAL FILING CHECKLIST FOR RESUBMISSION OF NDA 202,008, Amyvid

NDA Number: 202,008 **Applicant:** Avid **Submission Date:** October 7, 2011

Drug Name: Amyvid (Florbetapir F18 Injection) **NDA Type:** Amendment 018 (Resubmission)

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
	FORMAT/ORGANIZATION/LEGIBILITY				
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD format in EDR and DARRTS
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			M1 (general info and labels), M2 (clinical overview addendum and safety summary) and M5 (clinical reports, tables, figures and dataset of PT01 study).
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			"Reviewer guide" in M1.2
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
	LABELING				
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Proposed label in PLR format in PDF and WORD in M1.14.1.3
	SUMMARIES				
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			"Clinical Overview Addendum" in M2.5
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Summary of clinical safety update to SAE in M2.7.4
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	2 different imaging assessment studies with CD-based (PT01) and in-person training (A16)
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			"Benefits and risks" in section 6 of "Clinical Overview Addendum" in M2.5
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
	DOSE				
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	X			10 mCi (370 MBq) of Amyvid, ≤ 50 ug drug mass dose, effective dose 7 mSv
	EFFICACY				
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			PT01 with 5 readers (trained with Web-based reader training program) and 184 scans; A16 study

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	Content Parameter	Yes	No	NA	Comment
					with 5 readers (trained with in-person style) and 59 scans
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Original PT01 protocol in IND 79511 SN 124 and revised protocol in SN 128
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
	SAFETY				
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Summary of clinical safety update to SAE in M2.7.4
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	Not in the current submission, but it is in the original NDA
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	NME, no similar drug is marketed anywhere yet
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	The drug is an imaging agent and not a chronically administered drug
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			184 PET scans for validation of Web-based reader training program
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			No death since the original NDA. 3 SAE describe in Summary of Clinical Safety Updates to SAE in M2.7.4
	OTHER STUDIES				
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
	PEDIATRIC USE				

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Pediatric study waiver requested in the original NDA
	ABUSE LIABILITY				
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
	FOREIGN STUDIES				
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
	DATASETS				
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			JMP data (---.xpt document) of PT01 available
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
	CASE REPORT FORMS				
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			In M2.7.4 Summary of Clinical Safety Updates to SAE
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
	FINANCIAL DISCLOSURE				
38.	Has the applicant submitted the required Financial Disclosure information?	X			In M1.3.4
	GOOD CLINICAL PRACTICE				
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			In M5.3.5.3.3 for PT01 study and in M5.3.5.1.3 for AV45A16 study

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.
The application is fileable from the clinical point of view.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
There is no major potential review issue identified at this time. We may have information request (IR) during reviewing process.

Qi Feng, MD, PhD 11/01/2011
Reviewing Medical Officer Date

Clinical Team Leader Date

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Internal discussion questions:

1. Submit or provide the location the document with raw data of silver staining result of all subjects under autopsy in PT01 study with total 59 cases.

2. According to your proposed label in the October 7, 2011 NDA resubmission, section 6.1, the total number of subjects administered florbetapir in clinical trials totaled "N=496 patients" (520 administrations). We note that this is the same number of subjects and florbetapir administrations stated in section 6.1 of the label submitted on September 17, 2010 in your original NDA. Based on Module 2.7.4 of Amendment 018, we are aware of at least 3 subjects who were administered florbetapir between the date of your original NDA submission (September 17, 2010) and your NDA resubmission (October 7, 2011).

    a. Clarify the total number of the subjects administered florbetapir between September 17, 2010 and October 7, 2011.

    b. Modify section 6.1 of the draft label to account for the adverse reactions experienced by all subjects administered florbetapir prior to the date of your NDA resubmission (October 7, 2011). If there are other sections of the label that require revision based on the subjects administered florbetapir between September 17, 2010 and October 7, 2011, please update these sections before providing the updated draft label to FDA.

    c. Provide an updated Integrated Summary of Safety (Module 5.3.5.3 in accordance with 21 CFR 314.50(d)(5)(vi)) and Summary of Clinical Safety (Module 2.7.4 in accordance with 21 CFR 314.50(c)(2)(viii)) which accounts for all subjects administered florbetapir before October 7, 2011.

3. Provide a description of the responsibilities of the Clinical Research Organization (CRO) in study PT01. Clarify if the source documents for study PT01 reside with the CRO, with Avid Radiopharmaceuticals, or with some other entity.

4. Submit or provide the location of all eCRF of PT01 study.

    5. Submit or locate the analysis and raw datasets (xpt files) of PT01, A016, A009, and A008 studies with define.pdf.
    6. Submit or locate the results for subgroup analyses (e.g., analyses by gender, age, racial and others).
    7. Submit or locate the safety data (xpt files with define.pdf) with any updated information after the original submission.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QI FENG
03/14/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-008
Priority or Standard	Complete, class 2 response (resubmission)
Submit Date(s)	October 7, 2011
Received Date(s)	October 7, 2011
PDUFA Goal Date	April 7, 2012
Reviewer Name(s)	Qi Feng
Review Completion Date	March 6, 2012
Established Name	Florbetapir, 18-F AV-45
(Proposed) Trade Name	Amyvid
Therapeutic Class	Diagnostic molecular imaging agent
Applicant	Avid and Eli Lilly
Formulation(s)	*"AMYViD (Florbetapir F 18 Injection) is a sterile, non-pyrogenic radiopharmaceutical for intravenous injection supplied at a strength of 37-1900 MBq/mL (1.0-50.0 mCi/mL) Florbetapir F 18 at calibration, which contains 4.5 mg sodium ascorbate, USP, 0.1 mL dehydrated alcohol, USP, and 0.9 mL of 0.9% sodium chloride injection, USP, per mL of solution."*
Dosing Regimen	370 MBq (10 mCi)
(Proposed) Indication(s)	(b) (4) [redacted]
Intended Population(s)	Adult patients with cognitive dysfunction

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Abbreviations and Definition of Terms

18F-AV-45: 18F-AV-45 Florbetapir F 18, Amyvid
AD: Alzheimer's disease
AE: adverse event/adverse experience
CERAD: Consortium to Establish a Registry for Alzheimer's Disease
CFR: Code of Federal Regulation
CI: confidence interval
CMC: Chemistry Manufacturing and Controls
CR letter: Complete Response Letter
CRO: Clinical Research Organization
CT: computed tomography
eCRF: electronic case report form
F-18: fluorine-18
GCP: Good Clinical Practice
IHC: immunohistochemistry
IND: Investigational New Drug
IRB institutional review board
IV: intravenous
HC: healthy control
LCI: lower bound of confidence interval
MBq: megabecquerel
mCi: millicurie
MCI: mild congnitive impairment
mg: milligram
mL: milliliter
MRI: magnetic resonance imaging
mSv: millisievert
NC: cognitive normal older control
NDA: New Drug Application
PET: positron emission tomography
SAE: serious adverse event
SAS: Statistical Analysis System
SAP: Statistical Analysis Plan
SD: standard deviation
SOT: standard of truth
μg: microgram

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the current submission and original new drug application (NDA), this clinical reviewer recommends approval of NDA 202-008 (Amyvid) for the indication of β-amyloid detection in the brain with a positron emission tomography (PET) scan, if an agreement is reached on the revision of the currently proposed drug label.

This is the second review cycle for the NDA. The original submission was on September 17, 2010. After the priority review, FDA issued a Complete Response (CR) letter to the sponsor on March 17, 2011 with the major deficiencies related to the need to develop a reader training program suitable for the market place and also to validate the performance of the training program in an image re-read study. The proposed label, manufacturing deficiencies and other issues were also raised in the letter. The current submission, AV45-Amendment 18 (A18), is a response to the issues raised in the FDA CR letter.

The current submission contains the sponsor's response to the CR letter, a web-based reader training program in a laptop computer (not archived), and four (4) PET image re-read studies, including 18F-AV45-PT01 (PT01) study with the readers trained using the proposed reader training program.

In the PT01 study, the pre-specified success criteria for the primary and secondary objectives were achieved. Specifically, inter-reader and intra-reader agreement statistical outcomes were successful. The secondary objectives of sensitivity and specificity, based on the histopathology true standard, were also achieved (median sensitivity of 82% and median specificity of 95%). The web-based reader training program suggested improved inter-reader agreement compared to the original A05 report. However, the training method is not perfect. Notably, 6 of the 59 patients (about 10%) with histopathology results had scans that were read incorrectly

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(discrepancy to the SOT) based on median reads of the 5 readers. Overall, the web-based reader training program appears to be as solid as, or better than the in-person reader training method.

The sponsor has adequately addressed all the clinical issues in the CR letter and the sponsor's responses are acceptable and well justified.

1.2 Risk Benefit Assessment

Overall, the drug benefit exceeds the risks.

Amyvid is a PET agent for amyloid detection in the brain, but is not proposed for Alzheimer disease (AD) diagnosis. The clinical usefulness of the drug is limited. A 2008 FDA/CDER advisory committee addressed the question of potential usefulness of amyloid PET agents by stating that "*a 'negative' amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer's Disease (AD)……"* and *"such a test would probably be a powerful tool for future research."*[3] A negative scan for a subject with symptoms of progressive cognitive impairment indicates no significant β-amyloid deposition in the brain and is likely inconsistent with on AD diagnosis, therefore, the patient's clinician should more carefully search for other causes of cognitive deficits or dementia.

The original and current submissions of the NDA presented safety data for a total of 1,287 subjects who received the drug. No major drug-related safety trends were observed.

Radiation risk of the drug is minimal. US federal regulation, Nuclear Regulation Commission (NRC), requires the limit occupational radiation exposure to adults working with radioactive material to 50 mSv per year [4]. The radiation exposure from the drug is approximately 7 mSv for a dose of 370 MBq (10 mCi), which is within the safety limits.

There are significant promotional wordings and descriptions associated with using the test to make an AD diagnosis in the currently proposed label. The major potential risk of the drug is misuse of the scan for AD diagnosis. The final drug label needs to fully address the limitations

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of the drug utility, clearly describe the intended population and state no clinical usefulness for screening or diagnosis of AD. The clinical usefulness of the drug must not be overstated.

1.3 Recommendations for Postmarket Risk Management Activities

None at the present time

1.4 Recommendations for Postmarket Studies/Clinical Trials

None at the present time

2 Introduction and Regulatory Background

2.1 Product Information

Amyvid is a PET imaging agent developed for detection of ß-amyloid in the brain.

Fibrillar amyloid consists of insoluble fibrous protein aggregates. Abnormal accumulation of amyloid in the brain play a role in various neurodegenerative diseases, including AD, Parkinson's disease, transmissible spongiform encephalopathy, Huntington's disease, familial amyloid polyneuropathy and cerebral amyloid angiopathy. Brain amyloid deposition is also seen in some healthy elderly people with normal cognitive function.

Regarding the pathogenesis of AD, the formation of amyloid plaques and neurofibrillary tangles are thought to contribute to the degradation of neurons in the brain and the subsequent symptoms of AD, see Figure 1 below. One of the AD hallmarks is the accumulation of amyloid plaques between nerve cells (neurons) in the brain. Neurofibrillary tangles are insoluble twisted fibers found inside the neurons. The AD pathological diagnosis requires presence of BOTH amyloid plaques and neurofibrillary tangles. The current drug, Amyvid, is for detection of amyloid plaque only.

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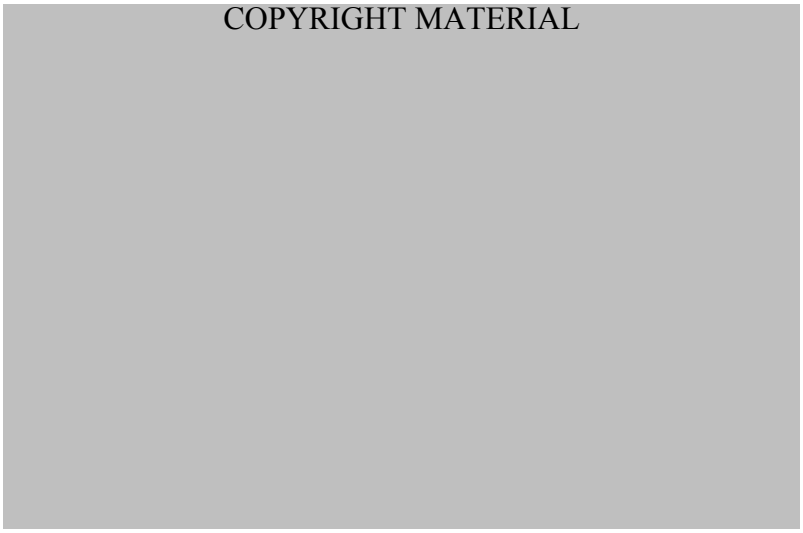
Figure 1: Plaques and Tangles



Online information, copied from American Health Assistance Foundation (AHAF) site
http://www.ahaf.org/alzheimers/about/understanding/plaques-and-tangles html

FDA/CDER sponsored a Peripheral and Central Nervous System Drugs Advisory Committee Meeting to discuss the development of amyloid imaging agent drugs on October 23, 2008. In the meeting, the committee agreed that a" negative" amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer's Disease (AD) and that histopathological correlation should be the "standard of truth" (SOT) in phase 3 clinical studies. [3]

The sponsor submitted the original NDA 202-008 on September 17, 2010. After 6 months priority review process, FDA issued a complete response (CR) letter on March 17, 2011. The current submission is a resubmission from the sponsor to response to the CR letter from FDA.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, no approved drug in the United States exists for detection of amyloid in the brain.

2.3 Availability of Proposed Active Ingredient in the United States

No additional information in the current submission

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2.4 Important Safety Issues with Consideration to Related Drugs

Based on the current submission and original NDA, the reviewer has not identified major safety issue for the drug.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Again, the sponsor filed the original NDA on September 17, 2010.

During the original review cycle:

The review team identified the following findings and major issues:

1. Amyvid binds to amyloid plaque and can be detected on a PET scan. There is a correlation between a semi-quantitative image read and the amount of amyloid present by histopathology (A07 study autopsy cohort).

2. The sponsor proposed 2 reading methods in the original NDA, semi-quantitative (0 – 4) and binary (negative or positive). During the review process, the sponsor proposed that the binary reading method would be the clinically applicable method if the drug is approved.

3. There was a relatively small brain autopsy sample size with only 35 subjects included in the application, and the clinically applicable (binary) read method was not fully used in the autopsy cohort; only 14 of 35 subjects with histopathology data had a binary PET image read results.

4. A phase 2 study (A05) enrolled age-matched healthy control subjects as well as patients with a diagnosis of mild cognitive impairment (MCI) and AD. However, the data raised questions about the inter-reader reproducibility of the binary read method. In A05 study, the reader unanimous agreement from the 3 readers for the entire 182 subjects was only 69%. For the MCI and age-matched healthy control subgroups, the agreements were 70% and 60%, respectively, see table below.

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Table 1: Inter-reader Agreement in the A05 Study

	A05 (3 Readers)	
	Image #	Unanimous agreement
Total	182	125 (69%)
AD	44	36 (82%)
HC	78	47 (60%)
MCI	60	42 (70%)

5. The major limitation was the lack of a validated reader training program that would assure a high degree of inter-reader agreement in the interpretation of the images. The scan appeared difficult to interpretate and it was thought to require a validated reader training program to educate the imaging clinician. The training program was not available yet.

Advisory committee meeting on the NDA:

FDA/CDER sponsored a Peripheral and Central Nervous System Drugs Advisory Committee Meeting to discuss the Amyvid NDA on January 20, 2011. In the meeting, the committee emphasized the importance of the development of the clinically applicable reader training program. It stated "*The committee members agreed that it is essential for there to be acceptable reader-to-reader reproducibility for the binary read method, based upon readers trained according to a clinically-applicable training program. The committee unanimously agreed that the available data support the approval of Amyvid if there were implementation of a training program that demonstrated accurate diagnosis within the autopsy standard/population (A07) and a demonstration of reader consistency in the population of intended application as exemplified by A05. In particular, they recommended that the sponsor provide additional data on inter-rater reliability (re-reading of the A07 and A05 scans using the binary method) prior to approval."* [5]

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FDA issued a CR letter to the sponsor on March 17, 2011 to raise clinical, product quality, labeling, facility inspections, safety update and other issues. One of most important issues was to develop a clinically applicable, web-base imaging reader training program with validation of the program.

The current submission contains the sponsor's response to the issues in the CR letter, the proposed web-base reader training program and 4 image re-read studies.

2.6 Other Relevant Background Information

No additional information in the current submission

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The reviewer has not identified quality and integrity issue. The Division of Medical Imaging Products (DMIP) has consulted the Division of Scientific Investigations (DSI) of CDER regarding site inspections for [redacted] (b) (4), an independent data vendor working as a Clinical Research Organization (CRO) for the PT01 study. [redacted] (b) (4) had made arrangement of all image randomization, developed and collected electronic case report form (eCRF) of the image re-reads by 5 individual readers from 5 different locations in the study. The reasons for the selected site inspection were the following:

1. A specific efficacy concern based on review of site specific efficacy data
2. A specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results.

3.2 Compliance with Good Clinical Practices

All 4 studies in the current submission are re-read of old PET image from prior studies A07 and A05 and no new subjects were enrolled or dosed for these studies. According to the sponsor's

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statement at the beginning of each individual study report, the studies submitted were *"approved by the relevant institutional review boards (IRBs) and conducted according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practice, or the applicable laws and regulations of the United States, whichever provided the greater protection of the individual."*

3.3 Financial Disclosures

According to the document of "*Disclosure: financial interests and arrangements of clinical investigators*" and Form 3455 in the submission (M1.3.4), there were two (2) investigators, (b) (6) [redacted], who received advisory fee less than $25,000 from the sponsor (Avid). Both of them were involved in (b) (4) study. (b) (6) [redacted] In January 2011, Eli Lilly purchased Avid; both of the investigators had previously received advisory fees from Eli Lilly for unrelated work. Together, the amounts exceeded $25,000 for both of them. Neither of them was directly involved in clinical interpretation of the images. The statistical analyses were performed by the sponsor.

Reviewer comment: The response and explanation are acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No additional information in the current submission

4.2 Clinical Microbiology

No additional information in the current submission

4.3 Preclinical Pharmacology/Toxicology

No additional information in the current submission

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4.4 Clinical Pharmacology

No additional information in the current submission

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There are 4 image re-read studies in the current submission. The readers in the studies were trained with 2 different training methods. The readers in the first 3 studies, 18-F-AV45-A08 (A08), 18-F-AV45-A09 (A09), 18-F-AV45-A16 (A16) were trained with in-person training and read the images in a core lab. In the 4th study, PT01, the readers were trained with the proposed web-based reader training program and the readers read the images in his or her own clinical settings. There were 151 subjects in the PT01 study: 59 autopsy subjects from A16, and 92 subjects from A05. Among the 92 subjects, there were 52 MCI, 20 age-matched normal controls and 20 with a clinical diagnosis of AD, see the summary table below.

Table 2: All Studies in the Resubmission

<table>
<tr><th>Study</th><th># of Readers</th><th colspan="2"># of Cases</th><th>Case Type</th><th>Training</th></tr>
<tr><td>A08</td><td>9</td><td colspan="2">35</td><td>Autopsy from A07</td><td rowspan="3">with the in-person training and read images in a core lab</td></tr>
<tr><td>A09</td><td>7</td><td colspan="2">40</td><td>AD and MCI from A05</td></tr>
<tr><td>A16</td><td>5</td><td colspan="2">59</td><td>Autopsy</td></tr>
<tr><td>PT01</td><td>5</td><td colspan="2">151</td><td>Autopsy from A16, NC, AD, MCI from A05</td><td rowspan="5">with the web-based training and read images in his own facility</td></tr>
<tr><td></td><td></td><td colspan="2">59</td><td>from A16</td></tr>
<tr><td></td><td></td><td rowspan="3">92</td><td>52</td><td>MCI from A05</td></tr>
<tr><td></td><td></td><td>20</td><td>NC from A05</td></tr>
<tr><td></td><td></td><td>20</td><td>AD from A05</td></tr>
</table>

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5.2 Review Strategy

The current submission contains the sponsor's response to all questions, comments and requests raised in the CR letter, the proposed web-based reader training program and the reports of 4 image re-read studies, A08, A09, A16 and PT01. Among the 4 studies submitted, only in the PT01 study were the image readers trained with the web-based reader training program which was requested by FDA; readers re-read the images in a format meant to simulate routine clinical practice. The readers in the other 3 studies were trained in a format with the in-person style and the images were re-read conducted in a core lab. Since the web-based training program will be the one for clinical implementation if the drug is approved for the market, the reviewer mainly focuses on this specific study. The reviewer will verify, analyze and evaluate all data submitted related to the training program, the validation of the program and updated drug safety data. The reviewer will also assess and analyze the sponsor's responses to the CR letter.

5.3. Discussion of Individual Studies/Clinical Trials

Please see review in Section 5.2 above.

6 Review of Efficacy

6.1 Indication

The currently proposed indication is as following:

(b) (4)

[redacted]

Reviewer comments: According to the 2008 Advisory Committee Meeting consensus, "positive" amyloid test would have very limited utility since cerebral

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amyloid is known to be present in multiple neurodegenerative conditions, including normal aging. Hence, the clinical usefulness of a "positive" amyloid test was regarded as tenuous (not useful). The currently proposed indication mentions (b) (4) **with a potential promotional purpose. Here is a very preliminary draft indication:**

(b) (4)

6.2 Efficacy Summary

Overall, the PT01 study data demonstrate satisfactory validation of the proposed web-based reader training program. The pre-specified success criteria for the objectives were achieved.

1. For the inter-reader agreement among the 5 individual readers, the Fleiss' kappa was 0.83 (95% CI: 0.78 to 0.88) for all 151 scans (59 autopsy, 20 age-matched healthy control, 52 MCI and 20 AD subjects).
2. For inter-reader agreements among the 5 readers in images of 59 autopsy and 52 MCI cases, the Fleiss' kappa values were 0.75 (95% CI: 0.67 to 0.83) and 0.93 (0.84 to 1.0), respectively.
3. For the 59 autopsy group, median sensitivity and specificity across the 5 readers relative to the pathology reference standard were 82% and 95%, respectively. However, for this subgroup, the readers trained with the web-based training program in the study PT01 had about 10% error rate (discrepancy of the image interpretation to the neuropathology result) at median read level, numerically higher than the readers trained with the in-person training in study A16.
4. For intra-reader (read and re-reread) agreement among the 5 readers in 33 mixed cases with different clinical diagnoses the median kappa values across the readers was 0.94 (95% CI: 0.82 to 1.0), and for 20 MCI cases, the kappa was 1.0.

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6.3 Methods

Study design:

The PT01 study was designed to validate the web-based reader training program.

1. Readers: Five (5) nuclear medicine physicians without prior experience in reading Amyvid-PET scans and blinded to the clinical information of the images.
2. Training: Readers went through the web-based reader training program within each reader's own site (typically 3 hrs). There were 3 modules in the program:

   Module 1: Amyvid for PET imaging of ß-amyloid plaques in the brain

   Reviewer comment: There are multiple promotional wording and sentences on AD diagnosis in the current version of module 1.

   Module 2: How to read Amyvid-PET scans with 5 demonstration cases and 7 practice cases. The goal was to provide an overall assessment of whether a PET scan is positive or negative.

   The key steps included:

   1). Display images in black and white with the maximum intensity set to the maximum intensity for the brain

   2). Review all transaxial images from bottom to top of the brain with reference to sagittal and coronal planes as needed

   3). On each slice, compare activity in cortical gray matter with activity in adjacent white matter

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Figure 2: Binary Reading: Negative

Negative: normally preserved gray-white contrast with the cortical activity less than the adjacent white matter.

Figure 3: Binary Reading: Positive

Positive: decreased gray-white contrast with increased cortical activity that is comparable to the activity in the adjacent white matter.

The criteria for a positive scan:

a) Two or more brain areas (each larger than a single cortical gyrus) with reduced or absent gray-white contrast;

Or,

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

Module 3: 20 self-assessment cases with answer keys.

The transcription of the web-based reader training program is submitted with the title "*16.1.10 Documentation of Inter-Laboratory Standard Methods*" at M5.3.5.3.13.

3. **Validation of the training program**: The design of the study was to evaluate the proposed training program. There were 5 nuclear medicine readers and they were blinded to all clinical information. The readers received training within the training program. Then the reader read images in his or her own clinical practice setting. All the images were randomized in 6 batches and a reader could only read 1 batch per day. Therefore, it took at least 6 days for the readers to finish reading all the images. There were 33 images read twice for intra-reader agreement assessment. There was to be no

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duplicate images in the same batch, therefore the reader would not read the duplicate on the same day. The 5 readers evaluated the images and reported their reading results to an independent data vendor, (b) (4), by electronic case report forms (eCRF).

The table 3 below shows the image sources and sample size setup. At the beginning, the sponsor proposed images of 119 subjects shown on the left side of the table, including 59 with autopsy and 60 from A05 with clinical diagnoses (20 each for cognitively healthy control, MCI and AD). The review team requested an increase in the MCI sample size since this subgroup of patients may be the most likely group to undergo the scan. The sponsor added 32 more MCI subjects and made final images of 151 subjects as shown on the right side of the table. The reason for 52 MCI cases rather than the original 60 cases is because 8 MCI cases images were used in the reader training program.

Table 3: Summary of the Image Sample Size Setups for the PT01 Study

Initially Planed				After Revision		
	Subject #	**From**			**Subject #**	**From**
Autopsy	59	A07 and A16		**Autopsy**	59	A07 and A16
HC	20	A05		**NC**	20	A05
MCI	20			**MCI**	52	
AD	20			**AD**	20	
Total	119			**Total**	151	

* HC = cognitively healthy control

Briefly, 5 readers interpreted 6 batches of total 184 old images from 151 subjects:

- 59 scans from A07 and A16 with autopsy data as SOT
- 92 scans from A05:
  - 52 subjects with clinical diagnosis of MCI
  - 20 subjects with clinical diagnosis of AD
  - 20 HC
- 33 duplicated scans from A05 for intra-reader agreement assessment
  - 20 MCI
  - 13 from AD and HC

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6.4 Demographics

The table below summarizes the demographics of the study PT01:

Table 4: Demographic and Other Baseline Characteristics

Characteristic	Primary Efficacy (n=119)	All Autopsy (n-=59)	Non-Autopsy A05 cases (n=60)	A05 MCI cases (n=52)	Autopsy Analysis (≤12 month Scan-to-Autopsy) (n=46)	A07 Autopsy (n=35)
Age (years)						
Mean (SD)	76.6 (11.8)	79.4 (12.6)	73.9 (10.3)	71.1 (10.6)	79.0 (12.4)	79.3 (13.3)
Gender: n (%)						
Female	59 (49.6%)	30 (50.8%)	29 (48.3%)	26 (50.0%)	21 (45.7%)	17 (48.6%)
Male	60 (50.4%)	29 (49.2%)	31 (51.7%)	26 (50.0%)	25 (54.3%)	18 (51.4%)
Race: n (%)						
Black	5 (4.2%)	3 (5.1%)	2 (3.3%)	2(3.8%)	3 (6.5%)	2 (5.7%)
Caucasian	111 (93.3%)	55 (93.2%)	56 (93.3%)	50 (96.2%)	42 (91.3%)	32 (91.4%)
Other	3 (2.5%)	1 (1.7%)	2 (3.3%)	0	1 (2.2%)	1 (2.9%)
Ethnicity: n (%)						
Hispanic	10 (8.4%)	5 (8.5%)	5 (8.3%)	11 (21.2%)	4 (8.7%)	2 (5.7%)
Non-Hispanic	109 (91.6%)	54 (91.5%)	55 (91.7%)	41 (78.8%)	42 (91.3%)	33 (94.3%)

* copied from the submission

6.5 Subject Disposition

6.5.1. Subject Disposition

No new subjects were enrolled in the PT01 study. All image and pathology data came from prior studies A05 and A07.

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6.5.2. Image Reader Disposition

There were 5 readers in the PT01 study. The brief educational background and working experience of the readers are as following table:

Table 5: The Reader Characteristics

Reader	Degree(s)	Residency Training		Fellowship	Title	Institution
1	MD, PhD	Internal medicine	Nuclear medicine	PET/CT	Assistant professor	Academic
2	MD	Radiology (non US)	Nuclear medicine	PET	Professor	Academic
3	MD	Radiology		Nuclear medicine	Director	Hospital
4	MD	Radiology		Nuclear medicine	Staff	Hospital
5	MD, MS	Neurology	Nuclear medicine		Staff	Hospital

All 5 readers in the study were well trained. Besides nuclear medicine residency or fellowship trainings, 3 of 5 readers had radiology residency trainings. Two of 5 readers had PET fellowship training and 1 reader had neurology residency training. There is no average education and professional training data for the nuclear medicine physicians in US available for comparison, but it is clear that all the 5 readers in the study were well trained.

6.6 Analysis of Primary Endpoint(s)

The primary objective of the PT01 was inter-reader binary read agreement for all images and different subgroups. The pre-specified success criteria for the primary objective was that Fleiss' kappa is ≥ 0.64 with the low bound of 95% CI ≥ 0.58.

The table below is kappa statistical analyses for all subjects and the different subgroups. For the initially designed 119 cases, revised 151 cases, 52 MCI subgroup, 59 autopsy subjects and 92 cases from A05, all the kappa values were greater than 0.64 with the low bound of 95% CI > 0.58. The primary objective was achieved.

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Table 6: Summary of the Inter-reader Agreement

	n	Fleiss' kappa	95% CI
Primary Analysis Population	119	0.81	0.75 to 0.87
A05 MCI cases only	52	0.93	0.84 to 1.0
All cases in study	151	0.83	0.78 to 0.88
All A05 cases	92	0.88	0.81 to 0.94
All autopsy cases	59	0.75	0.67 to 0.83

* copied from the submission

Table below shows that the kappa values for each individual reader relative to every other reader also exceeded the pre-specified target Kappa value of 0.64.

Table 7: Individual Reader to Reader Kappa Statistics

	Kappa (lower 95% CI)				
	Reader 1	Reader 2	Reader 3	Reader 4	Reader 5
Reader 1		0.87 (0.78)	0.83 (0.73)	0.78 (0.67)	0.83 (0.73)
Reader 2			0.73 (0.62)	0.85 (0.75)	0.83 (0.73)
Reader 3				0.75 (0.63)	0.83 (0.73)
Reader 4					0.81 (0.71)
Reader 5					

*copied from the submission

There were 92 subjects without autopsy in the PT01 study and all of them were from the A05 study. It is interesting to compare the reader agreement rate between the A05 study and the PT01 for the same image set (92 images) as shown in the Table 8 below. All 92 mages were from A05 image pool with established clinical diagnoses. There were 3 readers trained with the in-person training in A05 study. There were 5 readers trained with the web-based training program in the PT01 study. For the same 92 image set, the variable is inter-reader agreement, which is a unanimous agreement among the readers. Obviously, reaching a unanimous agreement among the 5 readers in PT01 is more difficult than the 3 readers in A05. In general, the unanimous agreement rates were higher for the PT01 study. Comparing PT01 to A05, for the same total 92 images, the agreement is 87% versus 72%, and for MCI subgroup, the agreement is 92% versus 67%, see table below:

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Table 8: Comparison of Reader Agreement in A05 and PT01 Studies

	Image Number*	Unanimous agreement by 3 readers in A05		Unanimous agreement by 5 readers in PT01
Total	92	66 (72%)		80 (87%)
AD	20	16 (80%)		14 (70%)
HC	20	15 (75%)		18 (90%)
MCI	52	35 (67%)		48 (92%)

* All images from A05 study

It is interesting to examine the consistency of the reading results (same reading results) from the A05 and PT01 studies for the same 92 subjects. Table 9 below shows that there was 68% [(28+5+30) / 92] consistency of the results from the readers trained by the 2 different training methods. The reviewer has noticed that the readers in the PT01 study tended to read more negative results than the readers in the A05 study for the same images. There were 25 cases with mixed reading results (positive and negative) by the 3 readers of the A05 study. However, 20 of these 25 cases were read negative unanimously by the 5 readers in the PT01 study.

Table 9: Comparison of Reading Consistency between A05 and PT01 Studies

		PT01 with 5 Readers			
		unanimous pos	pos and neg	unanimous neg	
A05 with 3 Readers	unanimous pos	28	6	2	
	pos and neg	0	5	20	
	unanimous neg	0	1	30	
					total 92

* All images from A05 study

In summary, the primary endpoint in the PT01 study achieved the primary objective. The results show the reader agreement improved compared to the A05 study.

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6.7 Analysis of Secondary Endpoints(s)

The secondary objective was to demonstrate the sensitivity and specificity of reader assessments using the web-based training. Sensitivity and specificity results are reported in all subjects who came to autopsy (all autopsy cases; n = 59) and in subjects who came to autopsy within one year of having a PET scan (n = 46).

For the autopsy group, the SOT is the neuropathology result based on the silver stain of the brain tissues. The neuritic plaque counts under the microscope were categorized using a semi-quantitative 4 point scales and the outcome converted further to a binary Consortium to Establish a Registry for Alzheimer's Disease (CERAD) diagnosis. The following table describes the conversion from neuritic plaque counts by silver stain to CERAD scales. Hence, a negative scan result could still contain 0 to 5 amyloid plaques.

Table 10: Conversion from Neuritic Plaque Counts by Silver Stain to CERAD Scales

Highest Neuritic Plaque Counts	CERAD Neuritic Plaque Scale
0	None
1 — 5	Sparse
6 — 19	Moderate
≥ 20	Frequent

The CERAD scales may convert to qualitative result of “none’ and “sparse” as negative and “moderate” and “frequent” as positive for amyloid. The sensitivity and specificity of the image interpretation were generated with CERAD binary results as the SOT and the PET image results in a 2 x 2 table.

For the secondary objective, the pre-specified success criterion was that the same 3 of 5 readers would achieve a lower bound of the 95% CI ≥ 0.50 for both sensitivity and specificity.

In the all-autopsy population (59 subjects, including PET to autopsy interval more than 12 months), all 5 readers achieved the specified success criterion of lower bound of 95% confidence interval for both sensitivity and specificity > 0.50, relative to the autopsy reference standard.

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The median sensitivity and specificity across the 5 individual reviewers relative to the pathology reference standard were 82% and 95%, respectively, see table below:

Table 11: All Autopsy Cases Population (n=59)

Reader	Sensitivity (95% CI)	Specificity (95% CI)
1	79% (64.5% - 89.2%)	90% (69.9% - 97.2%)
2	92% (79.7% - 97.3%)	90% (69.9% - 97.2%)
3	69% (53.6% - 81.4%)	95% (76.4% - 99.1%)
4	87% (73.3% - 94.4%)	95% (76.4% - 99.1%)
5	82% (67.3% - 91.0%)	95% (76.4% - 99.1%)

* copied from the submission

In the autopsy analysis population (46 subjects with PET to autopsy interval within 12 months), all 5 readers again achieved the specified success criterion. The median sensitivity and specificity across the 5 individual reviewers relative to the pathology reference standard were 89% and 93%, respectively, see table below:

Table 12: Autopsy Analysis Population (n=46)

Reader	Sensitivity (95% CI)	Specificity (95% CI)
1	86% (68.5% - 94.3%)	89% (67.2% - 96.9%)
2	100% (87.9% - 100%)	89% (67.2% - 96.9%)
3	75% (56.6% - 87.3%)	94% (74.2% - 99.0%)
4	93% (77.4% - 98.0%)	94% (74.2% - 99.0%)
5	89% (72.8% - 96.3%)	100% (82.4% - 100%)

*copied from the submission

6.7.1 The Cases with Disagreements between Pathology and Image Median Interpretation

Although the pre-specified success criterion was achieved, the training program is not perfect. It has a 10% failure rate, based on median reading results. Compared to the readers in A16 (trained with in-person training and assessed the images in a core lab) and for the autopsy group, the readers trained with the web-based training program had a numerically higher failure (imaging interpretation discrepancy to the neuropathology results) rate, see Table 13 below:

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Table 13: Reading Results for the Scans with SOT in the PT01 and A16 Studies

	PT01	A16
Patient #	59	59
Reader #	5	5
Total image #	295	295
Image read error (x / 295)	42 (14%)	30 (10%)
Patient read error (x / 59)*	6 (10%)	3 (5%)

* Based on median of 5 readers

There were 6 missed (incorrectly read) cases based on the median reading among the 59 autopsy cases according to the SOT in the PT01 study. Among the 6 missed calls, there was 1 false positive and 5 false negative cases compared to the SOT. For a more detailed analysis of the 6 missed cases, see Table 14 below. The letters and numbers marked in red indicate the incorrect reading compared to the neuropathology SOT. Among the 6 missed patients, five patients who had amyloid on SOT were read as negative (false negative on scans) and one patient who did not have amyloid by SOT was read as positive (false positive on the scan). As mentioned earlier, the positive amyloid test is not clinically meaningful. Only the negative scan result has clinical meaning. With a negative result, the patient's physician could more aggressively look for the treatable causes of the cognitive impairment or dementia. A perfect or ideal image reading is to read all truly negative cases correctly and avoid false positives. Here, we see only one false positive among the 6 missed cases.

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Table 14: Scans with Discrepancy between Pathology and Scan Interpretation

	Subject ID	PET to Autopsy Interval (month)	CERAD	PT01 Median	A16 Median
1	054-001	22	Pos	Neg (0+ / 5-)	Neg (0+ / 5-)
2	137-002	14	Pos	Neg (0+ / 5-)	Neg (0+ / 5-)
3	522-003	5	Pos	Neg (1+ / 4-)	Neg (2+ / 3-)
4	522-006	18	Pos	Neg (1+ / 4-)	Pos (4+ / 1-)
5	062-004	0	Pos	Neg (2+ / 3-)	Pos (4+ / 1-)
6	057-007	4	Neg	Pos (4+ / 1-)	Neg (2+ / 3-)

In summary for the secondary endpoint, the PT01 study objective was achieved. However, the readers trained with the web-based training program had a slightly higher error rate in the autopsy subjects compared to the readers trained with the in-person training of the A16 study.

6.8 Other Endpoints

6.8.1. Inter-reader Agreement in MCI Cases

The subjects with MCI are probably the intended population for the main use of the drug. Consistent interpretation of the images from this sub-population is important for the validation of the training program. Initially the sponsor proposed 20 MCI from A05. FDA requested all MCI in the image pool of the validation study making the final sample size of 52. The Fleiss' kappa of the inter-reader agreement among the 5 readers for all 52 MCI images was 0.93 (95% CI: 0.84 to 1.0), see Table 15 below.

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Table 15: Inter-reader Agreement in A05 MCI Cases (n=52)

	Positive Cases by Median Read N=17		Negative Cases by Median Read N=35		Overall N=52
Reader	Agrees to Median (N)	Percent Agreement	Agrees to Median (N)	Percent Agreement	Percent Agreement
1	15	88%	35	100%	96%
2	17	100%	35	100%	100%
3	16	94%	35	100%	98%
4	17	100%	34	97%	98%
5	17	100%	35	100%	100%

6.8.2. Intra-Reader Agreement of the Images with Mixed Diagnoses

Another concern is the intra-reader agreement (read and re-read by the same reader). There were 33 images from 151 subjects read twice by the 5 readers. This following table is the exploratory intra-reader agreement assessment for 33 images from A05. The result is good. The overall agreement was 96% and median kappa was 0.94. The results of the intra-reader agreement are good, see tables below:

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Table 16: Intra-reader Agreement of the Images with Mixed Diagnosis (N=33)

Reader	Observed Agreement (%)	Kappa (SR)	95% CI	*P*-value
1	94	0.87 (0.09)	0.70, 1	< 0.001
2	100	1 (0)	1, 1	< 0.001
3	91	0.80 (0.11)	0.58, 1	< 0.001
4	97	0.94 (0.06)	0.82, 1	< 0.001
5	97	0.94 (0.06)	0.82, 1	< 0.001
Overall / Median	96	0.94 (0.06)	0.82, 1	< 0.001

* modified from the submission

6.8.3. Intra-reader Reliability with MCI diagnosis

Table 17: Intra-reader Agreement of the Images with MCI Diagnosis (N=20)

Reader	Observed Agreement (%)	Kappa (SR)	95% CI	*P*-value
1	95	0.87 (0.12)	0.64, 1	< 0.001
2	100	1 (0)	1, 1	< 0.001
3	95	0.87 (0.12)	0.64, 1	< 0.001
4	100	1 (0)	1, 1	< 0.001
5	100	1 (0)	1, 1	< 0.001
Overall / Median	98	1 (0)	1, 1	< 0.001

* modified from the submission

The review team found that there was a minor protocol violation. According to the image randomization design for the intra-reader agreement assessment, the readers should not read an image twice on the same day. However, the data showed that there was one reader (reader 5) who read duplicated images from 3 subjects (6 images) on the same day. The images from the 3 subjects were in different batches and a reader should read maximally one batch per day. However, the reader read batches 1 and 2 on the same day. But overall, this reviewer does not consider that the quality of the intra-reader agreement is significantly compromised by the minor protocol deviation.

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6.8.5. Confidence Measures

Besides binary interpretation of the images, the readers were required to rate the confidence of the interpretation on a 3-point scale, low, medium and high and to select the specific criteria, see summary table below. Across all 151 scans, the two most frequent reasons selected for "low" confidence were "Atrophy" (n = 16), and "Image near the positive/negative threshold" (n = 15), which indicates the gray matter thinning (brain atrophy) and borderline images are the major challenges for the confident image interpretation.

Table 18: The Frequency of Low, Medium and High Confidence Cases

	Low	Medium	High
Primary Analysis (119 scans, 595 reads)	30 (5.0%)	115 (19.3%)	450 (75.6%)
A05 MCI Cases (52 scans, 260 reads)	8 (3.1%)	32 (12.3%)	220 (84.6%)
All cases (151 scans, 755 reads)	38 (5.0%)	136 (18.0%)	581 (77.0%)
A05 Cases (92 scans, 460 reads)	15 (3.3%)	63 (13.7%)	382 (83.0%)
Autopsy cases (59 scans, 295 reads)	23 (7.8%)	73 (24.7%)	199 (67.5%)

* copied from the submission

6.9 Subpopulations

No subpopulation analysis for the PT01 was submitted in the current submission. After FDA request for the information, the sponsor provided a summary table of the reader performance results by subject subgroup for study PT01, see below. As can be seen in the table, most subgroups are small and confidence intervals are wide. No meaningful differences between subgroups are observed for inter-reader reliability or reader performance in this study among individuals of different gender, race and age.

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Table 19: Subgroup Analysis of Inter-reader Agreement

Sub-Group	Kappa (95% CI) (N=151)	Sensitivity[a] (95% CI) (N=39)	Specificity[a] (95% CI) (N=20)	Accuracy[a] (95% CI) (N=59)
Gender	-	-	-	-
Male	0.81 (0.74, 0.88) n=76	76% (53%, 90%) 13/17	100% (76%, 100%) 12/12	86% (69%, 95%) 25/29
Female	0.85 (0.78, 0.92) n=75	95% (78%, 99%) 21/22	88% (53%, 98%) 7/8	93% (79%, 98%) 28/30
Age	-	-	-	-
< 65	0.92 (0.82, 1) n=34	75% (30%, 95%) 3/4	100% (57%, 100%) 5/5	89% (57%, 98%) 8/9
≥ 65	0.81 (0.75, 0.86) n=117	89% (74%, 96%) 31/35	93% (70%, 99%) 14/15	90% (78%, 96%) 45/50
Race	-	-	-	-
Caucasian	0.83 (0.78, 0.88) n=141	86% (72%, 94%) 32/37	94% (74%, 99%) 17/18	89% (78%, 95%) 45/59
Non-Caucasian	0.91 (0.71, 1) n=10	100% (34%, 100%) 2/2	100% (34%, 100%) 2/2	100% (51%, 100%) 4/4

CI=confidence interval
[a] based on the majority read.

6.10 Analysis of Clinical Information Relevant to Dosing Recommendations

No additional information submitted.

6.11 Discussion of Persistence of Efficacy and/or Tolerance Effects

No additional information submitted.

6.12 Additional Efficacy Issues/Analyses

6.12.1 The Complete Response (CR) Letter Issues

In the current submission, in addition to the web-based reader training program and image re-read validation studies, the sponsor has responded to all questions, comments or requests in the FDA CR letter. The reviewer assessed each sponsor's response below. [The issues outlined in the Complete Response letter are in ***bold*** *and italics*, followed by the sponsor's response to the specific issue in regular font.] The reviewer's comment is in the end of the section.

CLINICAL

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1. ***During the terminal portion of the review cycle (February, 2011), [Avid Radiopharmaceuticals] submitted revised labeling and two new study reports that described "reread" results for Study A07 and a selected portion of Study A05. Our examination of this information found that it did not sufficiently address our findings from a detailed review of the clinical data supplied within the original submission.***

Sponsor Response:
"Study A08 (NDA 202-008 amendment 013 dated 04 Feb 2011) and Study A09 (NDA 202-008 amendment 014 dated 16 Feb 2011) provide important data on reader performance using the binary read methodology intended for marketing implementation. However, A08 and A09 exclusively trained readers in-person, and image interpretations were done in a core laboratory setting. Following FDA consultation (see response 4d below for communication history), Avid has converted the training materials to a web-based, remote (i.e. not-in-person) self-study training format and has tested its performance in a larger blinded-read study of scans from autopsy (A07/A16) and non-autopsy (A05) subjects (Study PT01). This study allowed for both training and image reads to occur in the reader's usual image-reading environment, over the course of several weeks, simulating what would be expected in routine clinical practice. The PT01 Clinical Study Report (CSR) included in this resubmission summarizes the results of this important study. In addition, the Study A16 CSR provided in this submission includes image interpretation from all autopsy cases of subjects enrolled in the A07 pivotal study (a total of 59 autopsy cases). Study A16 was initiated prior to discussions with the FDA regarding PT01, and key design elements resulted from discussions with the European Medicines Agency. Furthermore, study A16 is relevant to FDA's CRL, which requested inclusion of all available autopsy cases and requested further testing of the binary read methodology. Study A16 used the same binary image interpretation methodology as Study PT01; however, training and image interpretation for Study A16 was conducted in-person at a centralized core lab. Results from A08, A09, A16, and PT01 are now summarized and compared to one another in a newly-created 2.5 Clinical Overview Update (referred to as 2.5 Addendum).

None of these four new studies involved any additional Amyvid doses to subjects or image acquisitions, but rather are comprised of re-reads of previously acquired images. A brief summary table appears below which describes the key features of each of these studies which applied the binary read methodology for interpretation of Amyvid-PET scans following the completion of a defined reader training program."

2. ***As discussed at the January 20, 2011 advisory committee, insufficient information has been submitted to support the approval of your application. The majority of committee members voted against approval at the present time and the discussion focused upon the need for the development of clinically-applicable reader training materials and verification of the reproducibility and reliability of image interpretations as performed in the clinicallyapplicable manner.***

Sponsor Response:
Avid has developed a qualitative visual binary PET scan interpretation methodology which has been applied in the blinded reading of PET scans in studies A08, A09, A16 and PT01. The binary read methodology has been refined and translated into a training process which has been

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successfully applied to both an in-person, centralized, core lab training environment (A08, A09, A16) as well as a web-based, self-study, remote training setting (PT01). As described in the 2.5 Addendum, Studies A08, A09, A16, and PT01 have consistently demonstrated high sensitivity and specificity and excellent inter-reader reliability, whether training was performed in-person or remotely via an automated computer program. Avid suggests that imaging physicians may be trained by either in-person or remote self-study processes in accordance with their own learning style preferences. Avid and Eli Lilly are prepared to provide such reader training support upon market clearance of Amyvid by FDA. The proposed training program materials for market implementation have been included on a portable laptop computer as part of this NDA re-submission for Amyvid.

3. ***Supply the reader training program materials you propose for marketing implementation. Portions of your submission referred to a potential website, to professional society training as well as other electronic media. Develop your training program materials in a manner that definitively establishes the elements of the program. This program should provide sufficient methods to help ensure reliable interpretation of Amyvid images and optimize image reporting. Submit the materials in a manner sufficient for our detailed review. We anticipate the need to incorporate these materials into labeling or another format that will preclude ad hoc modifications of the materials in the post-marketing setting. In addition to any other items, address the following topics within the program:***

Sponsor Response:
The reader training program materials intended for marketing implementation (including associated Amyvid-PET images) are being submitted to the agency on a computer laptop as part of this resubmission. This laptop contains two versions of the training program:

- The final version of the training intended for clinical implementation.
- The version of the training program used to train Study PT01 readers

This final version intended for implementation is identical to the PT01 training except that portions of Module 1 have been removed in response to comment 4a in the FDA Advice/Information Request Letter dated 10 June 2011.

a. ***Provide background on Amyvid, including a description of*** (b) (4) ***and how Amyvid can be used*** (b) (4) ***. Define*** (b) (4)

Sponsor Response:
Because of the ambiguity of the term (b) (4) the use of this phrase has been eliminated from the Indication and Usage statement and has been minimized in the training. The description of (b) (4) in the training now refers to neuritic plaque density categories (none/sparse, moderate/frequent) consistent with the indication statement and the internationally-accepted modified CERAD terminology.

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The background of Amyvid and the efficacy results describing how Amyvid can be used to detect moderate or frequent β-amyloid neuritic plaques in the brain are discussed in the Prescribing Information Section 2.5, and in the Label Justification Document, Part II. Amyvid as a Pathology Imaging Agent. The reader training materials provide a description of β-amyloid aggregates in Module 1 of the training program. Module 2 and Module 3 of the training describe how a physician interprets Amyvid images by the binary read method consistent with the neuritic plaque density categories (none/sparse or moderate/frequent).

b. ***Describe the strengths and limitations of Amyvid imaging, including its inability to diagnose any disease or condition, including Alzheimer's disease.***

Sponsor Response:
Module 1 of the Amyvid training program provided on computer laptop describes strengths and limitations of Amyvid imaging. The training specifically mentions that
Amyvid imaging alone is not an AD diagnostic, but rather it provides physicians with the information about the presence or absence of AD pathology in the brain.

c. Describe the procedures for interpreting Amyvid images, including any unique hallmarks or signals for distinction of a "positive" versus a "negative" image.

Sponsor Response:
The procedures for interpreting Amyvid images and criteria for distinction of negative and positive scans are included in the Prescribing Information Section 2.6, and in the Label Justification Document Part II. Amyvid as a Pathology Imaging Agent, as well as in the training program materials on the laptop computer included with this resubmission.

Briefly, scans which should be interpreted as negative show prominent white matter uptake with clearly lower uptake in adjacent cortical gray matter, allowing identification of clear gray-white contrast in all four brain lobes (frontal, temporal, occipital, and parietal). Scans which should be interpreted as positive have one or more areas with increased cortical gray matter signal which results in reduced (or absent) gray-white contrast.

d. Include a procedure for representative image display and a test image assessment.

Sponsor Response:
The electronic training modules include a visual check performed by the user to verify whether the user's monitor has adequate contrast for image review in the web-based training modules. Both the Prescribing Information Section 2.6 and the training materials (provided on laptop computer) include representative images and instructions for viewing images.

e. Describe the clinical meaningfulness of Amyvid image findings.

Sponsor Response:
The clinical meaningfulness of Amyvid image findings (as per the revised indication statement) is supported by discussion in the 2.5 Addendum, the Label Justification

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Document Part III. Negative Scan – Efficacy and Clinical Utility, and Part IV. Positive Scan – Efficacy and Clinical Utility and is summarized in Module 1 of the training.

f. ***Describe the procedure for reporting the image findings. We recommend the use of a template text that briefly summarizes the findings as well as the strengths and limitations of these findings.***

Sponsor Response:
Examples of radiology report image finding templates are included in the electronic training provided on the laptop computer for FDA review.

Additionally, it would be helpful to explain how the training program for marketing implementation evolved from the training that was utilized in the initial reads of study A05 and A07 and any subsequent reads utilizing a binary read methodology (studies A08 and A09).

Sponsor Response:
Evolution of the training is discussed in detail in the 2.5 Addendum Appendix Section 8.1.

4. Using the established reader training program materials, supply information from a study that reinterprets the images obtained in Studies A07 and A05. This study is necessary to establish the validity of the training program for marketing implementation. Study A08 and Study A09 are not sufficient because they do not employ the exact training materials and methods that will be used in clinical practice. Develop a protocol and conduct the study in a manner representative of image interpretation in the proposed clinical setting. Reader training methods for these studies should not extend beyond the materials included within the established reader training program.

Sponsor Response:
The PT01 CSR provides data validating a remote, web-based training program which used the binary read interpretation method established in Studies A08 and A09 and applied in Study A16. The PT01 study training was conducted independently by each reader in their typical image reading setting. The physician reviewers participating in this study were required to complete the training remotely, without assistance from Avid experts. Following training, the physician reviewers interpreted scans in their usual image-reading environment over a period of several weeks, thus imitating clinical practice workflow.

Study PT01 met all pre-defined success criteria for sensitivity and specificity, as well as inter-reader reproducibility and, therefore, successfully validates the binary image read methodology and the accompanying training materials.

a. Images of subjects in the autopsy cohort of Study A07 (at least 152 subjects, see 4.f. below) and all subjects in Study A05 (n=184) are expected to be randomized together in the reading queue for reinterpretation by each reader.

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The final study design of PT01 agreed to with the Agency involved the randomized, blinded reading of images from 151 subjects:

- 59 subjects who completed autopsy from A07/A16 (regardless of elapsed time between scan and autopsy)
- All 52 MCI subjects available from study A05 (excluding those subject scans used in the training materials)
- 20 AD subjects
- 20 cognitively-normal elderly subjects from study A05

b. In the development of the analytical plans for Study A07 images from subjects with histopathology, in addition to any other analyses, include an exploratory analysis of performance characteristics (sensitivity, specificity, correlates) in comparison to aspects of the autopsy truth standard relevant to your proposed clinical indication, e.g., the modified CERAD neuritic plaque density.

Sponsor Response:
An analysis of the performance characteristics in the autopsy populations was a key objective of Study PT01 and the results of these analyses are provided in Study PT01 CSR Section 11.3.2. In the autopsy analysis population of all 59 subjects for whom autopsies were available, median sensitivity was 82% and median specificity was 95%. In the autopsy analysis population which included only those subjects (46) who came to autopsy within one year of the Amyvid-PET scan, median sensitivity was 89% and median specificity was 94%. Regardless of autopsy population used, no individual reader sensitivity or specificity had a lower bound of the 95% confidence interval below 50%, meeting all pre-defined success criteria.

c. Plan for analyses that assess the reproducibility of image interpretations among the readers. Before initiating these studies, it is important that you discuss with us the number of readers to include in these studies and the success criteria.

Sponsor Response:
The analysis approach and number of readers for Study PT01 was discussed and agreed with the FDA in advance. The primary analysis evaluated the inter-reader reliability of the binary (positive vs. negative scan) rating among the 5 readers. The primary outcome variable was the overall inter-reader Fleiss' kappa statistic among the 5 readers. An overall Fleiss's kappa value of greater than 0.64 was required to meet the inter-reader reliability criterion (see statistical justification document for more details on the selection of this test and success criterion, expected confidence limits and power calculations). As reported in PT01 CSR Section 11.3.1, the study results met the predefined success criteria for inter-reader reliability (Fleiss' kappa 0.81 [95% CI: 0.75-0.87]).

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d. We strongly encourage you to submit the protocols for these studies for our review, prior to your initiation of the studies. Supply the protocols to your Investigational New Drug (IND) 79-511 application.

Sponsor Response:
The following communications occurred between Avid and the Division regarding the PT01 study (hyperlinks denote documents included in this resubmission):

- March 22 teleconference regarding in-person physician reader training
- March 24 teleconference regarding remote/web-based training of readers
- March 29 letter from Avid to FDA indicating Avid's willingness to attempt validation of remote/web-based reader training in Study PT01
- April 27 submission to IND #79,511 (serial number 0120) containing draft protocol for Study PT01
- May 11 FDA Clinical Information Request requesting submission of web-based reader training materials
- May 19 courier delivery by Avid to FDA of a computer containing draft web-based reader training materials
- June 10 email clinical advice letter from FDA with preliminary review comments regarding the April 27 protocol submission
- June 13 email from Avid to FDA DMIP with Avid agreement/responses to the June 10 FDA advice letter
- June 14 teleconference between Avid and the Division further discussing the FDA recommendations and Avid responses related to the acceptability of web-based training materials, the reader training protocol, and statistical design recommendations for the testing of reader training
- August 8 submission of Protocol PT01 to IND #79,511 (serial number 0124)
- August 29 letter with additional advice/recommendations from DMIP
- September 1 submission of Amendment 1 to PT01 protocol to include all available MCI images in the validation reading phase of the study as requested by the Agency (IND#79,511 serial number 0128).

e. The previous training programs for readers included hands on training and readings conducted at central facilities. For these studies, it is preferable that the readings not be conducted at a central lab or facility. We are interested in having the readings conducted in a manner and in conditions similar to what will occur with the marketing of the drug.

Sponsor Response:
Study PT01 tested the feasibility of training florbetapir-naïve imaging physicians on the binary image read method when conducted in a remote clinical setting via an automated, self-study process. All images were evaluated by the readers in a blinded and randomized fashion over a period of several weeks, in their usual clinical image-reading environment thus emulating a routine clinical practice workflow (Study PT01 CSR Section 9.4.2).

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f. The primary efficacy population for Study A07 is rather small, with only 29 subjects. Any additional data from patients originally enrolled in the autopsy cohort who have died since the submission of this application, should have brain histopathology analyzed and readings of their scans included.

Sponsor Response:
Study A16 and Study PT01 include analyses of a total of 59 Study A07 subjects who received an Amyvid-PET scan and consent for autopsy was obtained. Of these 59 autopsy subjects, 46 subjects came to autopsy within 12 months of the Amyvid-PET scan. This sub-population is analyzed separately for efficacy in A16 and PT01 CSRs because Alzheimer's disease is a progressive neurodegenerative disease and it is possible that significant accumulation of neuritic plaque could occur over periods longer than one year. For this reason, the scan-to-autopsy interval of ≤ 12 months was one of the principle criteria used in the A07 trial for defining the primary efficacy population.

5. During the review cycle, you modified your drug's proposed indication to state that it is indicated for (b) (4) ***The modified indication statement also notes,*** (b) (4)

a. Your NDA contained multiple amendments that were intended to support your drug's modified indication. However, the NDA did not contain a single cohesive, detailed description of the basis for the modified indication. For example, the amendment from December 2, 2010 appeared to rely upon a publication (Neurology 2005; 64:834; authored by Bennett) as the main support for your modified indication. Multiple other publications referenced throughout your application appeared pertinent to the modified indication. The multiple data sources were not organized and presented in a manner that allowed us to verify the appropriateness of your modified indication.

Sponsor Response:
A Label Justification Document is provided in Module 1.11.3. The Label Justification Document contains a detailed description of the basis for the indication with references supporting the indications and use. Additional analyses and discussion of reader performance obtained in Studies A08, A09, A16, and PT01 also appears in the 2.5 Addendum.

b. Supply a document that contains a detailed justification for your use of the phrase, (b) (4)

Sponsor Response:
The proposed revised indication is:

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(b) (4)

The rationale for this proposed Indication and Usage statement is discussed in the Label Justification Document as well as in the 2.5 Addendum included in this NDA resubmission. The proposed Indication and Usage statement has been modified based on the Agency CRL comments and the new data obtained as part of studies A16 and PT01. The terminology (b) (4) has been removed from the revised proposed Indication and Usage statement due to the noted ambiguity of such wording. The Label Justification Document Part I – Pathology of Alzheimer's Disease, provides a detailed discussion of neuritic β- amyloid plaques and the criteria used to generate a neuropathologic diagnosis of Alzheimer's Disease. The new Indication and Usage statement specifically refers to none/sparse or moderate/frequent plaque levels as per CERAD terminology in an effort to provide clarity to the bases for proposed efficacy and utility language in the revised proposed Prescribing Information included in this NDA resubmission.

c. ***Develop the justification document to include appendices of relevant publications and data sources. This information may importantly impact your labeling. As currently proposed, your labeling does not sufficiently define the phrase,*** (b) (4) ***and does not appear to contain sufficient justification for your proposal*** (b) (4) ***To illustrate one aspect of our concern, you refer to*** (b) (4) ***in a manner that appears to represent your interpretation of neuritic plaque densities assessed by histopathologic staining of brain tissue. If this is your interpretation, we anticipate that labeling would describe the neuritic plaque density observation, not use an inference to*** (b) (4)***.***

Sponsor Response:
The Indication and Usage section of the label has been updated to specifically describe the relationship between scan interpretation and neuritic plaque levels (none/sparse or moderate/frequent). Part I – Pathology of Alzheimer's Disease of the Label Justification Document provides the in-text sources and relevant publications describing how neuritic plaque levels are used in the post-mortem diagnosis of AD. Part III. Negative Scan – Efficacy and Clinical Utility describes how a negative scan result is inconsistent with a diagnosis of Alzheimer's disease.

d. ***It is important that labeling include a discussion of the limitations of Amyvid PET with regard to the diagnosis of Alzheimer's disease. Your revised labeling includes*** (b) (4)***. In Study A05, some healthy subjects and patients with mild cognitive impairment had images read as "positive" for amyloid. For those with mild cognitive impairment and a "positive" amyloid scan, it could be inferred that*** (b) (4)

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[redacted] (b) (4). You have not provided sufficient evidence to show that Amyvid may [redacted] (b) (4). Please provide a detailed justification for use of the phrase [redacted] (b) (4)

Sponsor Response:
In regards to the new label, there are several ways the limitations of Amyvid PET are noted. The indication specifically states the intended population have 'cognitive impairment being evaluated for suspected Alzheimer's disease' which clearly excludes healthy subjects. Also, the label indicates that "AMYViD is an adjunct to other diagnostic evaluations" and thus should not be used alone to make a diagnosis. Furthermore, the training indicates that "Some scans may be more difficult to interpret due to image noise, atrophy with a thinned cortical ribbon, or image blur. New users of AMYViD should be trained to ensure accurate and reliable interpretation of the PET images."

In regards to the request for more justification on this issue, Part IV – Positive Scan – Efficacy and Clinical Utility in the Label Justification Document provides a discussion of the clinical utility of a positive scan result and the limitations stating that Florbetapir-PET is not intended to be used by itself for a patient diagnosis. In the case of subjects suspected to have AD, a positive amyloid scan provides additional information for the clinician to include in his/her judgment of whether a given patient's cognitive impairment is of the Alzheimer's type (i.e. having evidence of AD pathology on the PET scan), thereby increasing the clinician's certainty in their final diagnostic determination of AD.

e. In addition to other items within your justification document:

i. Define the various types of amyloid plaques and the extent to which they are imaged with Amyvid;

Sponsor Response:
In the pivotal clinical study A07, the quantitative Amyvid PET signal (cortical average SUVR) was shown to correlate with total Aβ (as measured in the quantitative antibody-based immunohistochemistry assay) with a $\rho = 0.75$. The correlation of Amyvid PET SUVR to neuritic plaque levels (CERAD) showed a $\rho = 0.74$. It is not possible to separate the brain PET signal based on the form of β-amyloid plaque to which Florbetapir F 18 binds. However, the neuritic plaques represent the dominant form of β- amyloid deposits in the AD brain. Therefore, it is expected that diffuse plaques could contribute to only a minor extent to the total florbetapir- PET signal. In Study A07 and the extension Study A16, out of 59 autopsy subjects there was only one case which showed evidence of a predominant diffuse staining by IHC. Therefore, diffuse amyloid deposition without neuritic plaques is an infrequent finding. In addition, this case was rated as amyloid-negative by a majority of the blinded readers, which is consistent with the neuropathological assessment of no neuritic plaques and is consistent with the expectation that diffuse plaques are present at relatively low levels and do not materially contribute to the florbetapir- PET signal.

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Please also refer to Part I – Pathology of Alzheimer's Disease in the Label Justification document for a more detailed discussion of the neuropathological treatment of diffuse and neuritic plaques, as well as Part II – Amyvid as a Pathology Imaging Agent in the Label Justification Document which further discusses the in-vitro binding data of florbetapir F 18 to β-amyloid aggregates and β-amyloid neuritic plaques.

ii. Comment specifically upon Amyvid imaging of diffuse amyloid plaques and the extent to which any detection has pathological significance;

Sponsor Response:
The relationship between diffuse amyloid plaques defined in microscopic analysis and their molecular components has not been firmly established. In in-vitro studies at the molecular level, it has been shown that florbetapir
F 18 binds to β-amyloid in fibrillic form, as it occurs in neuritic plaques and possibly in diffuse plaques. There is no evidence that florbetapir F 18 binds to monomeric Aβ-peptide, the building block of β-amyloid, or to non-fibrillic Aβ-aggregates, which may be a component of diffuse aggregates. As discussed in the Label Justification Document, the neuritic plaque density is the foundation on which all neuropathology systems have been based. Diffuse plaques are not part of the criteria used for the neuropathological diagnosis under either CERAD or NIA-Reagan conventions. A recent expert review on AD and AD pathology (Selkoe 2011) illustrates the uncertainties associated with the definition of Aβ aggregates and supports our focus on neuritic plaques as the internationally-accepted and relevant form of Aβ deposits from a neuropathological perspective.

iii. Develop your (b) (4) discussion in a method conducive to potential incorporation of the major points into your drug's prescribing information.

Sponsor Response:
See response to 5b above.

f. Within the justification document clearly define the association among the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scoring of neuritic plaque density, any modification of this scoring and important contemporary criteria for the neuropathologic diagnosis of Alzheimer's disease. Present this material in a manner that cites the strengths as well as the limitations of the available data. Anticipate the potential need to incorporate the major points of this discussion within your drug's prescribing information.

Sponsor Response:
Part I – Pathology of Alzheimer's Disease in the Label Justification Document defines: 1) how the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) categorizes neuritic amyloid plaque levels as None, Sparse, Moderate, or Frequent, 2) the role of neuritic plaques as an essential component of the neuropathological definition of AD, and 3) why it has been maintained for over 25 years as an essential component in the neuropathologic assessment of AD pathology.

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6. In study A08, patient 057-007 had a CERAD score of "none" but 8 of 9 readers designated this as a positive scan for amyloid. Please explain how this occurred.

Sponsor Response:
The image from subject 057-007 was classified as Aβ+ by 8/9 raters in Study A08, 2/5 raters in Study A16 and 4/5 raters in Study PT01, but was classified amyloid negative (no neuritic plaques) at autopsy and was also negative by SUVR (SUVR=0.91). Discussion of this case is provided in a PT01 CSR Appendix. In the post-hoc review of the images at Avid there appears to be loss of gray-white contrast in the occipital lobe, but no other definite areas of gray-white contrast loss are seen. A single area with loss of gray-white contrast is negative, according to the established read methodology. However, there was some misalignment of the PET and CT images and it is possible that head motion may have made the image more difficult to interpret. The Prescribing Information Section 2.6 has been updated with additional guidance for readers noting scans may be more difficult to interpret due to high image noise, atrophy with a thinned cortical ribbon, or image blur due to head motion during the scan.

PRODUCT QUALITY

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LABELING

10. In the Highlights section of the label, revise the (b) (4) ***to the following:***

(b) (4)

Sponsor Response:
This information has been incorporated into the Prescribing Information, Highlights.

11. Modify the (b) (4) ***section, in Highlights as follows:***

(b) (4)

Sponsor Response:
This information has been incorporated into Prescribing Information, Highlights.

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13. ***In the package insert, revise section 8.1, Pregnancy to the following:***

- ***Pregnancy Category C:*** [redacted] (b) (4) ***Amyvid should be administered to a pregnant woman only if clearly needed.***

Sponsor Response:
This information has been incorporated into Prescribing Information Section 8.1.

13. **Modify** ***section 8.3, Nursing Mothers to the following:***

- [redacted] (b) (4)

Sponsor Response:
This information has been incorporated into Prescribing Information Section 8.3.

14. ***Revise section 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility to the following:***

- ***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*** [redacted] (b) (4) ***(19F-AV- 45, the non-radioactive form of florbetapir F 18). In a chromosomal aberration in vitro study with cultured human peripheral lymphocytes cells,*** [redacted] (b) (4) ***did not increase the percent 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*** [redacted] (b) (4) ***was evaluated in a mouse micronucleus study. In this assay,*** [redacted] (b) (4) ***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.***

  [redacted] (b) (4)

Sponsor Response:
This information has been incorporated into Prescribing Information Section 13.1.

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15. Submit draft labeling that incorporates the requested revisions cited above. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

Sponsor Response:
Requested Package Insert documents including SPL, summary of changes, clean version, and annotated version have been resubmitted in Module 1.

16. Submit draft carton and container labeling revised based upon the requested alterations, as listed above.

Sponsor Response:
The updated label is provided in Module 1 of this submission.

FACILITY INSPECTIONS

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SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

Sponsor Response:
There are no significant changes or findings in the Florbetapir F18 safety profile. There are no new finalized studies which have involved florbetapir administration since the original NDA submission (see Table 2 below). There have been 3 new treatmentemergent SAEs reported in the past year from ongoing studies. Avid concurs with the Principal Investigator assessments that there is an unlikely association with drug administration for these three SAEs. Avid has concluded that these events do not change the risk/benefit profile of florbetapir F 18 which was reported in original NDA 202-008. The narratives for these new SAEs may be found in the 2.7.4 Summary of Clinical Safety Update included with this NDA resubmission.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

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- ***Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.***

Sponsor Response:
See above – there are no new finalized studies of Amyvid since the original NDA.

- ***Present tabulations of the new safety data combined with the original NDA data.***

Sponsor Response:
See above response

- ***Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.***

Sponsor Response:
See above response

- ***For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.***

Sponsor Response:
There are no other indications other than the proposed indication.

3. ***Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.***

Sponsor Response:
There is no new information available regarding premature discontinuations.

4. ***Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.***

Sponsor Response:
There are no new completed studies involving new administrations of Amyvid.
Study A16 followed subjects who were dosed with Amyvid in Study A07. The remaining completed studies (A08, A09, PT01) involved re-reads of previously acquired Amyvid-PET images.

In the interval between NDA filing on 17-Sept-2010 and the date for re-submission cutoff 1-Sept-2011, there have been three additional treatment emergent SAEs from ongoing clinical studies. Two SAEs were reported in Study AV-133-B03, which is sponsored by Avid under IND # (b) (4); one SAE is from an investigator-sponsored study in France. SAE narratives for these three events are provided in the 2.7.4 Summary of Clinical Safety Update.

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5. ***Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.***

Sponsor Response:
There is no new information regarding substantial changes in the incidence of common, less serious adverse events to add to that reported in the original NDA.

6. ***Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time). Need to provide an update to subjects dosed as part of WW studies***

Sponsor Response:
The table below provides the total exposure to Amyvid in Avid-sponsored studies through 29 September 2011.There are seven ongoing studies of Amyvid sponsored by Avid being conducted under IND# 79,511, and one study (AV-133-B03) being conducted under IND# (b) (4).

Table 2: Amyvid Exposure in Avid-Sponsored Clinical Studies

Study number	Location	Number of Subjects Exposed	Study Status
A01	US	32	Complete
A02	US	9	Complete
A03	US	20	Complete
A04	US	25	Complete
A05	US	184	Complete
A07	US	226	Complete
A11	US	86	Ongoing
A12	US	27	Ongoing
A14	US	203	Ongoing
A15-ADNI-GO	US/Canada	268	Ongoing
ACRIN 1403	US	27	Ongoing
ADNI-2	US	137	Ongoing
010	UK	10	Ongoing
AV-133-B03[a]	US	31	Ongoing
Total		**1285**	

a Avid Study AV-133-B03 is being conducted under IND# (b) (4). Subjects receive scans using AV-133 and AV-45 (Amyvid)

As of 29 September 2011, there have been 290 subjects exposed to Amyvid in investigator-sponsored studies worldwide. All of these studies are ongoing.

As of 29 September 2011, there have been 1001 subjects exposed to Amyvid as a biomarker in studies of investigational therapeutics under INDs sponsored by other companies. All of these studies are ongoing.

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7. ***Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. Need to provide an update to subjects dosed as part of WW studies***

Sponsor Response:
As noted above, there are no new finalized studies since the original NDA has been submitted and Amyvid is not approved for marketing anywhere in the world.

8. ***Provide English translations of current approved foreign labeling not previously submitted.***

Sponsor Response:
Amyvid is not approved for marketing anywhere in the world. There are no approved foreign labels to submit at this time.

Reviewer's comments: The sponsor's responses are generally acceptable. The readers in the PT01 study were trained with the proposed web-based reader training program and the pre-specified success criteria for the primary and secondary objectives of the PT01 study were achieved. However, the currently proposed label and the reader training program need to be revised significantly due to multiple promotional wordings and sentences.

6.12.2 Other Opinion on the Drug Efficacy/Analysis

An organization named "Public Citizen" (http://www.citizen.org/Page.aspx?pid=183) mailed FDA a letter which cited the editorial article titled "*Amyloid-β imaging with PET in Alzheimer's disease: is it feasible with current radiotracers and technologies?"* [6] In the paper, the authors concluded "*…… amyloid imaging agents in detecting AD are not justifiable*". The authors appear to assume and misunderstand that the indication of the drug Amyvid would be "detecting of AD". But from perspective of this clinical reviewer, Amyvid is for detection of amyloid in the brain, not for diagnosis of AD. As mentioned earlier, abnormal amyloid deposition is not specific to a certain disease. Abnormal accumulation of amyloid in the brain appears to play a role in multiple neurodegenerative diseases, including AD. Brain amyloid deposition is also seen in some healthy elderly people with normal cognitive function. The 2008 FDA/CDER advisory committee addressed the question of potential usefulness of amyloid PET agents, "*a 'negative' amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer's*

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Disease (AD)……" [3] In the drug label, the description of relationship of the amyloid and AD diagnosis must be well balanced to avoid misleading the clinicians and patients.

7 Review of Safety

Safety Summary

Safety data from original and current submissions with total 1,287 subjects shows no important safety issue for the drug.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety population in the original NDA was 496 subjects. However, studies have been ongoing for various treatment drugs where Amyvid was given to the patients. In the current submission, the sponsor submitted the serious adverse event (SAE) reports of an additional 791 subjects in the ongoing studies. Therefore, there have been 1,287 adult subjects who received at least one administration of the drug, see summary table below:

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Table 20: Subject Exposure in Avid-Sponsored Clinical Studies

Study Number	Number of Subjects Exposed	Safety Data Included in NDA and Resubmission
Completed Studies		
A01	32	All
A02	9	All
A03	20	All
A04	25	All
A05	184	All
A07	226	All
Total Completed:	496	
Ongoing Studies (Avid monitored studies		
A11	86	SAEs only
A12	27	SAEs only
A14	203	SAEs only
A17	2	SAEs only
ACRIN 1403	27	SAEs only
10	10	SAEs only
AV-133-B03	31	SAEs only
Ongoing Studies (NIA/ADCS-monitored studies)		
A15-ADNI-GO	268	SAEs only
ADNI-1	137	SAEs only
Total Ongoing	791	
Completed plus Ongoing total	1,287	

*modified from the submission

7.1.2 Categorization of Adverse Events

No additional information in the current submission

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Please see the review in the section 7.1.1 above.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety data from 1,287 subjects is adequate for a medical imaging product.

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7.2.2 Explorations for Dose Response

No additional information in the current submission

7.2.3 Special Animal and/or In Vitro Testing

No additional information in the current submission

7.2.4 Routine Clinical Testing

No additional information in the current submission

7.2.5 Metabolic, Clearance, and Interaction Workup

No additional information in the current submission

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No additional information in the current submission

7.3 Major Safety Results

There is only SAE data available for the new 791 subjects who are still in the ongoing studies. The safety data in the original submission showed that among the 496 subjects, the most commonly reported adverse event was headache, which was reported in approximately 2% of the subjects with administration of the drug. Among the 496 subjects in the original submission, there were 4 serious adverse events (SAE) reported, including 2 deaths. But, none of the serious adverse events appeared related to the drug.

7.3.1 Deaths

Among the new 791 subjects in the current submission, there were 3 serious adverse events (SAE) reports, including one death. The cause of death was considered un-related to the drug. The subject was an 84 year old female with a diagnosis of dementia with Lewy bodies who was enrolled in a therapeutic drug study. There were no complications during the imaging procedure and 24-hour postdose. One week later, she was lucid. The subject died 10 days post the drug

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administration. The cause of death remains unclear. The investigator found this event to be remotely (unlikely) related to study drug. This observation appears consistent with the relatively short half-life of the drug.

7.3.2 Nonfatal Serious Adverse Events

There were 2 other serious adverse events (SAE) reports among the new 791 subjects. The first subject was a 62 year old female with a clinical diagnosis of AD who was enrolled in a therapeutic drug study. She slipped on a wet surface and had acute right patella fracture 3 weeks post the drug administration. The second SAE was a 73 year old male with smoking history was diagnosed as "bladder cancer" 10 months after the drug administration. The cause of the SAE of both cases were considered un-related to the drug.

7.3.3 Dropouts and/or Discontinuations

No additional information in the current submission

7.3.4 Significant Adverse Events

No additional information in the current submission

7.3.5 Submission Specific Primary Safety Concerns

No additional information in the current submission

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

No additional information in the current submission

7.4.2 Laboratory Findings

No additional information in the current submission

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7.4.3 Vital Signs

No additional information in the current submission

7.4.4 Electrocardiograms (ECGs)

No additional information in the current submission

7.4.5 Special Safety Studies/Clinical Trials

No additional information in the current submission

7.4.6 Immunogenicity

No additional information in the current submission

7.7 Additional Submissions

No additional information in the current submission

8 Postmarket Experience

No post-marketing data exists since the drug has not been marketed yet.

9 Appendices

9.1 Literature Review/References

1. CFR 21 Part 315 Diagnostic radiopharmaceuticals 2009 http://law.justia.com/us/cfr/title21/21-5.0.1.1.5.html

2. Guidance for industry Developing medical imaging drug and biological products Part 2: Clinical indications. 2004 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071603.pdf

3. FDA/CDER Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting October 23, 2008 http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4382m1-Final.pdf

Reference ID: 3098290

4. Fact Sheet on Biological Effects of Radiation in NRC website http://www.nrc.gov/reading-rm/doc-collections/fact-sheets/bio-effects-radiation.html

5. FDA/CDER Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting January 20, 2011 http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM244441.pdf

6. Moghbel, MC, et al. Amyloid-β imaging with PET in Alzheimer's disease: is it feasible with current radiotracers and technologies? Eur J Nucl Med Mol Imaging. 2011 Oct 19. [volume and page pending] http://www.ncbi.nlm.nih.gov/pubmed/22009379

9.2 Labeling Recommendations

The major concerns regarding the proposed label and the web-based reader training program include the following:

1. There is a significant attempt [redacted] (b) (4) in the proposed label, which might mislead clinicians and patients. All the promotional descriptions, tables and graphs in the label should be eliminated.

9.3 Advisory Committee Meeting

FDA/CDER sponsored a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to discuss the NDA 202-008 (Amyvid) on January 20, 2011. The followings are the major highlights from the Meeting Minutes:

"Questions to the Committee:

1. (Discussion: New Considerations) In 2008, the PCNS Drugs Advisory Committee concluded that "a negative amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer's Disease." Before turning to consider Amyvid™ specifically, discuss any new scientific and clinical developments since 2008 that bear on the clinical utility of a reliable imaging assessment "for the detection of cerebral amyloid."

Committee Discussion: *The committee members felt there have been major advances, especially in mild cognitive impairment (MCI) patients. There was a general consensus that there has been additional scientific research since 2008 which is supportive of the prior recommendations on the clinical utility of a negative scan for amyloid in patients with symptoms consistent with dementia.. Additionally, the committee agreed that the new research offers a stronger evidentiary base for the recommendations from the 2008 advisory committee meeting. The*

Reference ID: 3098290

committee was informed by the sponsor that the proposed indication had changed during the review cycle to state that, "Florbetapir F18 injection is a diagnostic radiopharmaceutical indicated for positron emission tomography (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." Certain committee members expressed the opinion that a negative amyloid test may not necessarily rule out amyloid presence but simply make amyloid presence less likely.

2. (Discussion: Image Read Methods) Two Amyvid™ image reading methods were used in the phase 3 trial (A07): a semi-quantitative scoring method (0 – 4) in the "autopsy" cohort and a "binary" (positive/negative) method in the "specificity" cohort. Only the binary method is proposed for the clinical use of Amyvid™. Discuss the strengths and limitations of the A07 trial data. Consider the following questions:

    a. To what extent would reinterpretation of the A07 "autopsy" cohort images help allay any concern about the lack of binary read results for patients with a histopathological measure of amyloid?

Committee Discussion: *The committee members concurred that the reinterpretation of the A07 autopsy cohort images by a number of readers who use a binary read method would be important for addressing concerns regarding the lack of data and also help address concerns regarding consistency among readers, particularly if the readers use the clinically applicable training methods .*

    b. How important is the establishment of a clinically relevant histopathological "threshold" for determining whether an image is positive/negative?

Committee Discussion: *The committee members agreed that a threshold must be chosen, but voiced concerns that the binary read method and the training in this method needs to minimize the potential for false positives and false negatives as well as inconsistency between image interpretations due to insufficient training. There was general consensus that there is a need for a clinically relevant histopathological "threshold" for determining whether an image is positive/negative.*

    c. How important is the establishment of a clinically-applicable reader training program?

Committee Discussion: *The committee members agreed that it is essential for there to be a clinically-applicable reader training program. Multiple committee members emphasized the need to verify the sufficiency of the reader training methods. Members generally did not favor a certification-type approach to the training procedures.*

    d. How important is the establishment of acceptable reader-to-reader reproducibility for the binary read method, based upon readers trained according to a clinically-applicable training program?

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Committee Discussion: *The committee members agreed that it is essential for there to be acceptable reader-to-reader reproducibility for the binary read method, based upon readers trained according to a clinically-applicable training program.*

3. (Discussion: Clinical Population) A phase 2 trial (A05) enrolled healthy control subjects as well as patients with a diagnosis of mild cognitive impairment or Alzheimer's Disease. However, the phase 2 data raise questions about the reader-to-reader reproducibility of the binary read imaging results. Discuss the strengths and limitations of the A05 data. Consider the following questions:

    a. To what extent does the A05 population exemplify patients who may ultimately undergo Amyvid™ imaging?

Committee Discussion: *The committee members agreed that the A05 population better exemplifies patients who may ultimately undergo Amyvid imaging.*

    b. To what extent would reinterpretation of the A05 images provide useful information, especially if the reinterpretation was performed by readers trained according to a clinically-applicable reader training program?

Committee Discussion: *There was a general consensus that reinterpretation of the A05 images will assess reproducibility of image interpretation among readers, and could increase confidence in the readings. The committee members agreed that there is important information to be gained in understanding the consistency of reads utilizing the scans of the A05 patients as a database.*

4. (Vote) Do the available data support the approval of Amyvid™ at the present time? Discuss the basis for the vote, including any database deficiencies and ways to resolve these deficiencies (such as the collection of new premarketing or postmarketing data).

    YES: 3 NO: 13 ABSTAIN: 0

Committee Discussion: *The committee members agreed that Amyvid does what it purports to do: That is, it allows for amyloid imaging. However, they voiced concerns regarding the inconsistency in the PET scan readings and the other deficiencies as outlined above. Thus, the committee encouraged FDA to review additional data resulting from implementation and testing of a reader training program aimed at improving reader consistency.*

5. (Vote) If there were implementation of a training program that demonstrated accurate diagnosis within the autopsy standard/population and a demonstration of a reader consistency in the population of intended application such as exemplified by A05, would the available data support the approval of Amyvid?

    YES: 16 NO: 0 ABSTAIN: 0

Committee Discussion: *The majority of the committee members requested the addition of this fifth question so that they may voice their desire to see Amyvid approved contingent upon*

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additional data and resolution of the reader training method concerns. The committee unanimously agreed that the available data support the approval of Amyvid if there were implementation of a training program that demonstrated accurate diagnosis within the autopsy standard/population (A07) and a demonstration of reader consistency in the population of intended application as exemplified by A05. In particular, they recommended that the sponsor provide additional data on inter-rater reliability (re-reading of the A07 and A05 scans using the binary method) prior to approval." [5]

Reference ID: 3098290

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/s/

QI FENG
03/07/2012

RAFEL D RIEVES
03/07/2012
have read and understand the points

Division of Medical Imaging Products

Medical Officer Memo

Date	17 March 2011
NDA	202008
Supporting Document (SD)#	13 and 14
Sponsor	Avid
Date of Submission	SD13: 04 February 2011, received 07 February 2011 SD 14: 16 February 2011, received 16 February 2011
Drug Product	Amyvid (Florbetapir F18 injection)
Intended Use	Amyloid detection
Clinical Reviewer	Lucie Yang, DMIP/ODE IV/OND/CDER

The sponsor submitted two amendments after the January 2011 Advisory Committee meeting which included clinical study reports for Study A08 and Study A09.

Study A08, was a reinterpretation of select Study A07 images by 9 readers. Study A09, was a reinterpretation of select Study A05 images by 7 readers. The readers were trained using lectures and training cases. The sponsor did not submit all of the training materials. From the brief description of the reader training method in the submission, it appears that there was significant human interaction and case-by-case feedback during the training. According to the submission, one individual "demonstrated the steps required to interpret the case using PowerPoint slides and the MIM workstation."

It is unclear whether the training method used for Study A08 and A09 can be implemented successfully through a training program using only electronic media which the sponsor has proposed to develop due to the extensive human interaction required in the training that was used to train readers for Study A08 and Study A09. It is highly unlikely that the training of readers in Studies A08 and A09 will be mimicked by the training that will occur in clinical practice.

The sample size is quite limited for both Study A08 and A09, and there appears to be more variability for images of subjects in the intended population in Study A09 than for end of life subjects in Study A08.

For the reasons stated above, Study A08 and A09 are not sufficient to validate the reader training program for Amyvid that will ultimately by implemented in clinical practice.

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LUCIE L YANG
03/17/2011

Office Director Decisional Memo

Date	March 17, 2011
From	Charles J. Ganley, M.D.
Subject	Office Director Decisional Memo
NDA #	202008
Applicant Name	Avid Pharmaceuticals, Inc.
Date of Submission	September 17, 2010
PDUFA Goal Date	March 17, 2011
Proprietary Name/Established (USAN) Name	Amyvid Florbetipir F18 Injection
Dosage Form	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	The indication statement was changed by the sponsor during the review cycle. The latest proposal (February 2011) was: (b) (4)
Action	Complete Response

Introduction

Amyvid is a PET imaging agent developed to detect ß-amyloid in the brain. ß-amyloid is found in patients with a diagnosis of Alzheimer's disease but it can also found in subjects who have no cognitive impairment. In these latter individuals, it is not clear that the presence of ß-amyloid is a predictor of future risk of developing the disease. If this drug is approved, it will be to detect amyloid and not to diagnose Alzheimer's disease.

Chemistry, Manufacturing and Controls

There is no outstanding chemistry or microbiology review issues. Six manufacturing facilities have a withhold recommendation after inspection.[1]

Nonclinical Pharmacology/Toxicology

There are no outstanding pharm/tox issues. In vitro and ex vivo studies verify that Amyvid binds to aggregated amyloid within the human brain. Some genotoxicity potential was identified by in vitro

[1] manufacturing facilities in Philadelphia, PA, PETNET manufacturing facilities in Kent, WA, Palo Alto, CA and North Wales, PA and Cardinal Health, manufacturing facilities in Charlotte, NC and Orlando, FL

studies (Ames/peripheral lymphocyte) but these observations are not supported by in vivo findings. The drug was assessed as having no significant genotoxicity risk. A waiver was granted for repro-tox studies.

Clinical Pharmacology

There are no outstanding clinical pharmacology issues. Amyvid is metabolized by the liver and excreted predominately through the biliary system. The radioactive isotope of the drug is fluorine-18, which decays by positron emission with a half-life of 110 minutes. Based on distribution and washout data, 30 – 50 minutes post-dose is recommended for imaging.

Clinical Microbiology

There are no outstanding microbiology issues.

Clinical Efficacy

The sponsor conducted multiple clinical studies to support the NDA. Table 2 in Dr. Dr. Feng's review briefly outlines the studies. My summary will focus on two studies, A05 and A07. Study A07 was the only phase 3 study conducted by the sponsor. The study attempted to correlate PET images with amyloid pathology. It enrolled two cohorts of patients. The "autopsy cohort" was comprised of adults with a projected life expectancy ≤ six months. These patients underwent PET imaging with Amyvid, and for those who died during the study follow-up, autopsies were conducted and the amount of amyloid in the brain was quantified by immunohistochemistry (IHC).[2] The young cognitively intact cohort included adults ≤ 40 years of age without risk factors for Alzheimer's disease. This cohort served as negative controls.

Three readers viewed each scan in a blinded fashion. In the autopsy cohort, the PET images were read using a semi-quantitative method in which scans were rated on a five point scale as 0 – 4 (with 0 = none, 4 = high). The median score of the three readers was used in the analysis that compared the PET image score to the amount of amyloid detected by quantitative IHC (the truth standard). Another rating scale was used to measure the amyloid burden in 6 areas of the brain.[3] In the cognitively intact cohort, the scans were read by three readers but were scored using a binary scale as being positive or negative for amyloid.[4] Many other analyses were conducted on the data in both cohorts.

Twenty-nine subjects were included in the analysis of the autopsy cohort.[5] The analysis comparing the semi-quantitative read (using the **median** of the three reads) and the quantitative IHC yielded a significant correlation with a Spearman's $\rho = .78$, $p < .0001$. When the semi-quantitative median rating and the IHC % are converted to a binary value (positive – negative) post-hoc, the sensitivity was 85% and the specificity was 100% using the median reads. (Feng at 30) These numbers are misleading because one of the readers had a sensitivity of 55%. This raises questions about the reproducibility of the PET image reads in clinical practice. (Yang at 9)

Forty-seven cognitively intact subjects, presumed to have negative amyloid status, were found to have negative scans. The sponsor claims the specificity to be 100%.[6]

Additional post-hoc analyses of the autopsy cohort were conducted where the median read were given a binary interpretation of positive or negative [7] and compared to a NIA-Reagan score. NIA-Reagan

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[2] Silver staining was also conducted and was used to assess the amyloid burden for use in determining the NIA-Reagan Alzheimer's disease probability and CERAD (Consortium to Establish a Registry for Alzheimer's Disease) scoring

[3] three point scale from 0 (no amyloid) – 2 (high)

[4] These scans were given to the readers in a blinded fashion and mixed with 40 scans from individuals from the autopsy cohort (to maintain some blinding) who had a median score of 2 or greater. The readers of the autopsy cohort were different from the readers of the young cognitively intact cohort.

[5] Six front runners were not included in the analysis but were used to help assist in training for subsequent reads.

[6] In all cases except for one, the readers agreed

[7] Semi-quantitative scores of 0 or 1 were negative and scores of 2 – 4 were characterized as positive.

is derived from silver staining and gives a no, low, intermediate or high probability for Alzheimer's disease based on amyloid and neurofibrillary tangle burden. This analysis suggests a high sensitivity and specificity in the autopsy cohort. (Feng at 29) The PET image / NIA-Reagan analysis was a post-hoc analysis and difficult to interpret because low burden was considered negative. There was no analysis in the reviews where low presence of amyloid by NIA-Reagan was considered a positive result. Also, the results utilized the **median** score to obtain the binary interpretation of the images. Additionally, Amyvid is not a test for Alzheimer's disease but a test for amyloid. The presence of amyloid alone is not sufficient to make a diagnosis of Alzheimer's disease. Study A05 demonstrated that cognitively normal people can have positive scans for amyloid. This finding does not make a diagnosis of Alzheimer's nor does it provide information that these subjects with go on to develop Alzheimer's disease. This will be important to convey in labeling should the drug be approved.

The clinical and statistical reviewers raised numerous problems with these analyses and how it should be interpreted.

- The autopsy cohort was small which leads to wide confidence intervals for the analyses. (Huang at 7)
- The **median** read value masks the individual reader performance. (Huang at 7)
- High correlation of the reads does not imply good sensitivity and specificity. (Huang at 36) The performance between individual readers is inconsistent which does not provide sufficient evidence of clinical usefulness. (Huang at 38)
- A detailed analysis of individual reader rating of amyloid burden on PET images demonstrates that the **median rating** obscures the high inter-reader variability among the three readers. (Feng at 19) The sensitivity of the individual readers range from 55 – 85% with wide confidence intervals. (Huang at 26)
- The young, cognitively intact cohort was assumed to have a negative amyloid status. Despite mixing positive scans with these scans, readers may have been un-blinded because CT scans would not have shown atrophy in this young population compared to the CT scans from the older patients with "positive" PET scans that were used to maintain some semblance of blinding. (Feng at 19)
- The cognitively intact cohort may not reflect the population in whom this drug will be used so it may not be an adequate measure of specificity. (Feng at 20; Huang at 7)
- In the autopsy study, 24% (8 of 29) of the subjects had a different binary read between the three reviewers. Based on histopathology, 31% (9 of 29) of the subjects had at least one reader interpret the PET image incorrectly. If all patients in the autopsy cohort are considered, 34% (50 of 147) of the patients had one reviewer with a different binary read than the other two readers. Nine of 147 patients had 1 reader rate the scan as zero for amyloid and at least one other reader rate the scan as a 3 or 4. (Yang at 10)

In study A05, PET images using Amyvid were performed on 78 healthy controls, 60 subjects with mild cognitive impairment and 45 subjects with a diagnosis of Alzheimer's disease. All subjects were > 50 years of age. There was no gold standard to assure the image interpretation was accurate so the only data of interest in this study is the agreement between readers. Binary reads of positive or negative were conducted. Using the majority read,[8] 14% of healthy controls, 38% of the mild cognitive impairment cohort and 76% of the Alzheimer's disease cohort had a positive scan. (Yang at 12)

The percentage of subjects where there was reader disagreement was 39.7% in the healthy cohort, 30% in the mild cognitive impairment cohort and 20% in the Alzheimer's disease cohort. The agreement between readers in the healthy cohort in study A05 was less than in the healthy cohort in study A07 which raises concerns about the general applicability of specificity results observed in study A07. (Huang at 29) The healthy controls in study A05 are more likely to be representative of the population that will be imaged if this drug is approved. As such, it is disconcerting that the reader agreement seems to be worse

[8] At least 2 of the 3 readers gave the same read.

than that observed with the younger population. The agreement between individual readers ranged from 63 – 91% in the healthy cohort, 70 – 98% in the mild cognitive impairment cohort and 84 – 91% in the Alzheimer's disease cohort. (Huang at 30)

Clinical Safety

No significant safety issues were identified.

Advisory Committee

- The sponsor informed the committee that the indication changed during the review cycle, "Florbetapir F18 injection is a diagnostic radiopharmaceutical indicated for positron emission tomography imaging of beta amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out presence of pathologically significant levels of beta amyloid in the brain."
- The advisory committee recommended reinterpretation of study A07 using a binary read method using readers trained with a clinically applicable training method.
- The committee did not recommend approval of the application until a clinically validated training program was developed and available.
- The committee did not recommend a mandatory training program.

Neurology Consult

The neurology consultant had similar concerns about the reading of the scans that have been raised in the DMIP and statistics reviews. In addition, they raised important issues regarding how this scan may be used in clinical practice if it were to be approved.

- This scan cannot diagnose Alzheimer's disease. Even within this application, positive scans were found in the healthy cohort within study A05 but these subjects did not have any cognitive impairment.
- If we can feel confident that a negative scan can be accurately read, then this will help to rule out significant deposition of amyloid. A clinician may be inclined to take this information and use it accordingly in coming up with a clinical diagnosis.
- The result of this scan does not preclude other testing that is necessary to evaluate a patient with mild cognitive impairment or dementia. The neurology consult raised this concern because some clinicians may be inclined to order this test without other appropriate testing.
- There have been efforts in the Alzheimer's disease field to diagnose stages of the disease earlier in the preclinical or prodromal stage. Use of this test in this context has not been validated.

Summary

- Amyvid binds to amyloid and can be detected on PET scans.
- The drug detects amyloid and can not make a diagnosis of Alzheimer's disease.
- There is a significant correlation between a semi-quantitative image read and the amount of amyloid present by histopathology (A07 autopsy cohort). This, however, does confer good sensitivity and specificity for all reviewers. The young cohort in study A07 does not provide sufficient reassurance that there is high specificity because they are not the population who will be studied if the drug is approved. There was high agreement between readers for this cohort. But, the reader agreement in study A05, which included the population likely to have this test, was dismal.
- The results of the autopsy study illustrate how important these types of studies are in the evaluation of drugs that image amyloid. Without the histopathology, the accuracy of the image readings would not be known. Only 35 subjects with brain histopathology are included in the application. As a consequence, the sensitivity and specificity assessed using this data has wide confidence intervals.

- Unlike a clinical trial, the scans will be read by a single reader in clinical practice. The current data clearly suggest that there could be significant variability among the readers. Because the scans are going to be read as positive or negative rather than another method (such as SUVR[9]), there are going to be errors in interpretation that possibly lead to changes in the management of patients. The training program utilized in the studies had variable degrees of intensity that will not be replicated if the drug is marketed. Even with this intensive training, however, the lack of consistency between readers in A05 and A07 is not reassuring.
- There are significant problems with reader agreement in the interpretation of the scans. These scans are difficult to read and will require a validated reader training program.
- A validated reader training program has not been submitted to the application.
- The populations likely to have this diagnostic test are patients with mild cognitive impairment and patients with dementia. For patients with mild cognitive impairment, a negative test may have some clinical utility but a positive test seems to have limited interpretability because there is no data in the application to address this issue. This is certainly not a screening test in patients who are cognitively normal because the result of the test is unlikely to provide predictive value of the future occurrence of a disease.
- There is one inspection to be completed and five facilities have withhold recommendations.

Conclusion

I agree with the division that the application should receive a complete response. The major limitation is the lack of a validated training program that would assure a high degree of reader agreement in the interpretation of the images. If this is not attainable using a positive/negative approach for reading, alternative methods of reporting the results will have to be explored.

[9] Standardized uptake value ratio

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/s/

CHARLES J GANLEY
03/17/2011

Summary Review for Regulatory Action

Date	February 21, 2011
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	202008
Applicant Name	Avid Radiopharmaceuticals, Inc.
Date of Submission	September 17, 2010
PDUFA Goal Date	March 17, 2011
Proprietary Name / Established (USAN) Name	Amyvid™ Florbetapir F18 Injection
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 statement was changed by the sponsor during the review cycle. The latest proposal (February, 2011) was: (b) (4)
Action/Recommended Action:	Complete Response: main issues pertain to the need for development of Amyvid image interpretation methods

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 & Anthony Mucci, PhD (TL)
Pharmacology Toxicology Review	Sunday Awe, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Ravindra Kasliwal, PhD & Eldon Leutzinger, PhD
Microbiology Review	Stephen Langille, PhD
Clinical Pharmacology Review	Christy John, PhD & Y. Moon Choi, PhD (TL)
DDMAC	Not consulted during this review cycle
DSI	Anthony Orencia, MD

CDTL Review	Dwaine Rieves, MD
OSE/DMEPA	Denise Baugh, PharmD & Todd Bridges, PharmD (TL)
OSE/DRISK	Suzanne Berkman-Robottom/meeting for 2/24/11
Pediatric and Maternal Health	Tammie Howard, RN & Karen Feibus, MD (TL)
Project Manager	Sharon Thomas, MS
Neurology Consultatnt	Nicholas Kozauer, 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

1. Introduction:

Avid Radiopharmaceuticals submitted a New Drug Application (NDA) to support the marketing of Amyvid™, a radiopharmaceutical imaging agent (F18 positron emission tomography drug). During the review cycle, the company changed the proposed indication to the following (as of February, 2011):

(b) (4)

This review cycle was particularly complicated by three major issues that were identified early during the review cycle and importantly impacted the advisory committee discussion that was held on January 20, 2011. To facilitate the review and to try to resolve these issues, the division met with the applicant on three occasions (face to face meetings). Still, the following issues were not fully resolved:

-the original application did not clearly indicate the clinically-applicable Amyvid image interpretation methods;

-the application did not sufficiently describe the clinically-applicable Amyvid interpreter training materials;

-once the applicant defined the clinically-applicable image interpretation methods during the review cycle, it became apparent that these methods were not sufficiently applied to the single confirmatory study and data were lacking regarding the reproducibility of image interpretation using these clinically-applicable methods.

These items form the main focus of our proposed Complete Response letter in which we request the submission of reader training program materials and a reread of certain images in order to help validate the reader training program sufficiency as well as the reproducibility of Amyvid image interpretation. In summary, the applicant's phase 3 study verified the ability of Amyvid to detect amyloid aggregates in the brain but the study image interpretation methods are not those proposed for clinical use.

My review document is finalized at a time point when the team has a meeting planned with the Office of Surveillance and Epidemiology/Division of Drug Risk Management in order to discuss the potential role of post-marketing requirements and/or a Risk Evaluation and Mitigation plan. The outcome of this meeting may ultimately impact our proposed Complete Response letter.

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 insoluble complexes (aggregated amyloid, predominantly a beta-sheet conformation). Amyvid has been shown to bind predominantly to aggregated amyloid within "neuritic" plaques of the human brain; the extent to which Amyvid binds to aggregated amyloid within "diffuse" brain plaques is unclear and is an outstanding question to the applicant. 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 the 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. 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 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 had Alzheimer's Disease.

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), an autopsy was performed to detect amyloid within the brain. This single phase 3 study provided the main support for this NDA.

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed mainly by Dr. Ravindra Kasliwal. The microbiology review was performed by Dr. Stephen lanignelle. The reviewers verified acceptable manufacturing procedures and recommended approval—once certain contingencies were addressed (acceptable labeling and acceptable facility inspections). At the present time, the facility inspection system (EES) is recommending a "with-hold approval" status. Some manufacturing facilities have been found to have an acceptable inspectional status but at least one site is deficient. The manufacturing reviewers are working to identify this site and clarify the nature of the deficiencies.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the Dr. Sunday Awe, the pharmacology/toxicology reviewer who noted that there are no outstanding pharm/tox issues that preclude approval, beyond the development of acceptable labeling.

In vitro and *ex vivo* studies verified that Amyvid 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 that there are no outstanding clinical pharmacology issues that preclude approval, although approval is contingent upon developing acceptable labeling. 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.

6. Clinical Microbiology:

The 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 provided the main statistical review. Dr. Lucie Yang provided a secondary clinical review. The reviewers noted that the primary endpoints in the single phase 3 clinical study were met; however, the phase 3 study image interpretation methods were not assessed as sufficiently supportive of Amyvid market/clinical usage.

Dr. Feng and Dr. Yang did not recommend approval based predominantly upon the image interpretation limitations cited above (lack of reader training program and insufficient evidence of reproducibility of image interpretation). The reviewers did not identify any notable safety findings beyond the risks associated with unreliable image interpretations.

Dr. Huang's review noted evidence of inconsistency among reader interpretations of Amyvid images; her findings importantly contributed to the team's concern about the need for further assessment of image interpretation reproducibility, based upon the use of a clinically-applicable reading method.

The following is a brief summary of the efficacy (phase 3) data.

Design: 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.

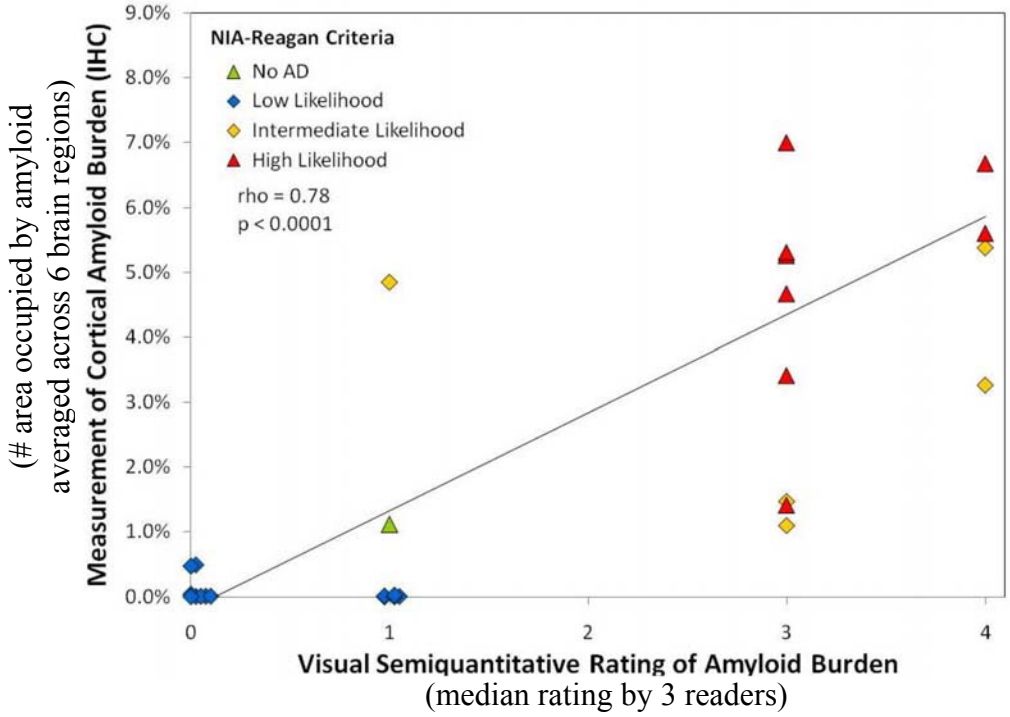
Reference standard: Histopathology was used to unequivocally determine amyloid burden for the autopsy cohort. Patients who expired within one year of PET imaging underwent autopsy. Quantitative histochemistry (IHC) was used to determine the average percent area occupied by amyloid averaged across six 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" $\geq$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 $\rho=0.78$, $p<0.0001$. 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.

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.

Post-marketing Requirements (PMR): At the present time, the review team is conceptualizing a need for a PMR trial that helps assess the sufficiency of the reader training program; the timeliness of completion of this trial will likely prove important to modification of the program to enhance its effectiveness.

9. Advisory Committee Meeting:

This 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 at the present time; deficiencies related to image interpretation methods, as noted above.

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:

DSI inspection of the phase 3 clinical data detected no deficiencies. Overall, the review team was consistent in its perspective that additional data and information must be supplied to support Amvid's approval. A Complete Response letter will describe these deficiencies.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAFEL D RIEVES
02/21/2011

CLINICAL FILING CHECKLIST FOR NDA 202-008, Amyvid

NDA Number: 202-008 **Applicant:** Avid **Submission Date:** Sept 17, 2010

Drug Name: Amyvid (Florbetapir F18 Injection) **NDA Type:** New drug application

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
	FORMAT/ORGANIZATION/LEGIBILITY				
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD format in EDR and DARRTS
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			M1 (general info and labels), M2 (preclinical and clinical summaries) and M5 (clinical reports, tables, figures and datasets)
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			"Reviewer guide" in M1.2
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
	LABELING				
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Draft label in PLR format in M1.14.1
	SUMMARIES				
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			"Clinical summary" in M2.7
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			"Summary of clinical safety" in M2.7.4
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			"Summary of clinical efficacy" in M2.7.3
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			"Benefits and risks" in M2.5.6
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
	DOSE				
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?	X			10 mCi (370 MBq) of Amyvid, ≤ 50 ug florbetapir F-19 (drug mass dose), effective dose 7 mSv
	EFFICACY				
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			One pivotal Study: 18-F-AV-A07 and the report in M2.5.4.1
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on	X			

	Content Parameter	Yes	No	NA	Comment
	proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Original INDs 76-852 and 79-511 (I 76852 was an Exploratory IND)
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			All 34 centers in the pivotal trial are in USA
	SAFETY				
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			"Summary of clinical safety" in M2.7.4
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			"ECG findings" in M2.7.4.4.2
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	NME, no similar drug is marketed anywhere yet
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	Amyvid is an imaging agent and not a chronically administered drug
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			35 patients for histopathology study and 496 subjects for safety
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			Integrated summary of safety (ISS) in M5.3.5.3
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	NME, no similar drug is marketed yet
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			One death in the pivotal trial (A07) and another in outside of the sponsor-supported trial (used as biomarker in a therapeutic trial) in M2.7.4.2.1.2
	OTHER STUDIES				
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			CRFs of death, SAE and AE in M5
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
	PEDIATRIC USE				
28.	Has the applicant submitted the pediatric assessment, or	X			Pediatric study waiver

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 202-008, Amyvid

	Content Parameter	Yes	No	NA	Comment
	provided documentation for a waiver and/or deferral?				requested in M1.9.1
	ABUSE LIABILITY				
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
	FOREIGN STUDIES				
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	All 34 centers in the pivotal trial are in USA
	DATASETS				
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			In M5
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
	CASE REPORT FORMS				
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			CRFs of deaths, AEs and SAE requested by the division in M2.7.4, appendix 9.2
	FINANCIAL DISCLOSURE				
38.	Has the applicant submitted the required Financial Disclosure information?	X			In M1.3.4
	GOOD CLINICAL PRACTICE				
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			In M5.3.5.1.3.5.2

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

The application is fileable from the clinical point of view.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There is no major potential review issue identified at this time. We may have information request (IR) during reviewing process.

Qi Feng, MD — 10/08/2010
Reviewing Medical Officer — Date

Alex Gorovets, MD
Clinical Team Leader — Date

CLINICAL FILING CHECKLIST FOR NDA 202-008, Amyvid

Filing Initial Clinical Review

NDA:	202-008, SN 01
Related INDs:	76-852 and 79-511
Product:	Amyvid **(**Florbetapir F18 Injection)
Sponsor:	Avid
Proposed indication:	*"Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β-amyloid, a defining pathology of Alzheimer's disease (AD)."*
Submission Date:	09/17/2010
NDA filing meeting:	10/14/2010
NDA midcycle meeting:	11/18/2010
AC meeting on the NDA:	01/20/2011
FDA PDUFA Date:	03/17/2011

Reviewer: Qi Feng, MD
Review Date: 10/8/2010

Introduction

Alzheimer's disease (AD) is the most common form of dementia and it is an incurable, degenerative, and terminal disease. Most often, this is diagnosed in people over 65 years of age. According to the Alzheimer's Association's "2009 AD Facts and Figures," 5.3 million Americans are living with AD.

The cause and progression of AD are not well understood yet. Research indicates that the disease is associated with plaques (primarily composed of amyloid beta peptides) and tangles in the brain.

AD is usually diagnosed clinically from the patient history, family history, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alternative conditions. Currently, CT or MRI and FDG PET are used to help exclude other cerebral pathology or subtypes of dementia.

Pittsburgh compound B (PIB) is a fluorescent analog of thioflavin T, which can be used in PET scans to image beta-amyloid plaques in neuronal tissue. Due to this property, PIB may be used in investigational studies of amyloid.

Amyvid is a diagnostic radiopharmaceutical indicated for PET imaging of amyloid in the brain. The non radioactive drug of Amyvid is an analog of PIB. The radioactive isotope of the drug is fluorine-18 with halflife of 110 minutes. The sponsor has conducted several phase I, II and III clinical trials under INDs 76-852 and 79-511.

CLINICAL FILING CHECKLIST FOR NDA 202-008, Amyvid

AC meeting on amyloid imaging trials design: There was a Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee on 10/23/2008 for discussion of clinical development of PET tracers for the detection of amyloid to assist in the diagnosis of AD. On the question of "*To what extent, if any, would an indication for the use of an in vivo diagnostic radiopharmaceutical agent for the "detection of cerebral amyloid" provide useful clinical information?"* The committee agreed that *a negative amyloid test could have clinical utility in ruling out a diagnosis of AD. Additionally, the committee noted that a positive test would only be supportive in the diagnosis of AD and would not provide a definitive diagnosis. Some committee members noted that a positive test could be use to help characterize AD, but not to diagnose it. The committee agreed that such a test would be a powerful tool for future research."*

AC meeting for this NDA: There will be an AC meeting scheduled on 01/20/2011for independent advice and recommendations to the FDA on scientific and technical matters related to this NDA.

Regulatory History:

1. Exploratory IND 76-852 was filed on 01/08/2007 (withdrawn on 02/14/2008)
2. Pre-IND and then IND 79-511 was filed on 03/06/2008
3. Pre-NDA meeting on 07/19/2010
4. NDA 202-008 was filed on 09/17/2010
5. Reproductive toxicology waiver was requested and FDA granted on 04/13/2010.
6. Carcinogenicity testing waiver was requested on 07/26/2010 (IND 79-511 SN085) and the decision pending
7. Pediatric testing waiver was requested on 03/09/2010 (SN 059) and the decision pending
8. Priority review was requested on 06/17/2010 (SN 078) and decision pending.

> ***Reviewer comment:*** *According to the FDA guideline "Review Classification Policy: Priority (P) and Standard (S)" MAPP 6020.3 [1] , the review classification is determined based on whether the drug product provides safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement compared to marketed products in treating, preventing, or diagnosing disease. To qualify for the priority review, the preliminary estimates should "indicate that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following: (1) safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products (approved, if approval is required), including nondrug products or therapies." Our preliminary review shows there is evidence to accept the request based on the reasons below:*
>
> 1. *AD is a uniformly fatal disease.*
> 2. *There is a large patient population in US.*
> 3. *Amyloid is thought to be involved in the pathogenesis of AD and there is no amyloid imaging scan in the market. The scan might be helpful as a conjunctive tool for diagnosis and research of AD if approved.*

Overview of the Submission

1. New NDA submission with specific categories described on the checking list above
2. Four phase I, one phase II and one pivotal phase III trials for efficacy (phase III trial) and safety, see table below:

Efficacy and Safety Studies Completed

Type of Study	Clinical Study Trial	Subject Distribution		Total	Major Finding
Phase I	A01	16 HC	16AD	32	PET shows AD > HC
	A02	9 HC		9	Radiation dose similar to FDG
	A03	11 HC	9 AD	20	Diagnostic quality: 370 MBq > 111 MBq
	A04	10 HC	15 AD	25	Test-retest shows excellent reproducibility
	A06	*From A01 + A03*		41	Scans at 30 and 50 min yield same results
Phase II	A05	79 HC	60 MCI 45 AD	184	PET beta-amyloid measures increase with dx (AD>MCI>HC), age, APOE4 and early cognition changes
Phase III	A07	74 HC	152 at end-of-life	226	Autopsy Cohort: Significant correlations between PET and pathological measures of beta-amyloid Specificity Cohort: High (100%) specificity

The pivotal phase III trial (18-F-AV-45-A07)

Title: A Phase III study of the correlation between florbetapir F 18 (18F-AV-45) positron emission tomography imaging and amyloid pathology

Design: A blinded study designed to test the correlation and agreement between measurements of amyloid by the drug PET imaging and levels of amyloid determined by histopathological analysis at autopsy

Centers: 34 centers in US and 25 of which enrolled at least 1 subject (1 – 25 subjects)

Objectives:

1. Test relationship between measurements of amyloid burden using Amyvid PET imaging and levels of amyloid burden determined at autopsy.
2. Test the specificity of Amyvid-PET to accurately identify the absence of amyloid pathology

Subjects: A total of 226 subjects were enrolled, 152 subjects in the autopsy cohort and 74 young healthy volunteer in the specificity cohort

Inclusion criteria:

1. Autopsy cohort: life expectancy of ≤ 6 months subjects
2. Specificity Cohort: Cognitively and neurologically healthy male and female subjects, 18 to 40 years of age, who had no known risk factors for AD

Drug Dose and administration

1. 10 mCi (370 MBq) Amyvid, ≤ 50 ug of florbetapir F-19 (mass dose of non radioactive drug substance) and the radiation exposure effective dose 7 mSv
2. IV bolus administration, single dose

CLINICAL FILING CHECKLIST FOR NDA 202-008, Amyvid

Imaging acquisition:

1. Brain PET scan for 10 minutes at 30 - 50 min post the tracer injection

PET imaging assessment:

1. Three independent readers (trained nuclear medicine physicians) of core lab for PET and histopathology correlation and another 3 readers for the specificity study of the drug
2. Qualitative scoring from 0 (no amyloid in the PET imaging) to 4 (severe amyloid) and quantitative measurement standard uptake value ratio (SUVR), the ratio of cortical to cerebellar signal

Histopathology tests:

1. Core Tissue Processing - brain dissection and tissue processing
2. Central Core immunohistochemistry (IHC) – for tissue section staining with the monoclonal antibody 4G8 to amyloid
3. Central Core Bielschowsky – for Bielschowsky silver staining
4. Neuropathologist (b) (4) – for evaluation of histopathology of brain tissue blindly

Efficacy result (preliminary, the NDA is under extensive review):

1. **Primary Correlation:** A significant correlation between the median of the blinded reader semi-quantitative visual ratings of amyloid detected on the Amyvid-PET image and the cortical amyloid level as assessed by quantitative IHC (average percent cortical grey matter area of amyloid on the IHC slides).

2. **Primary Specificity:** A good specificity of Amyvid-PET imaging from the independent reader (majority) qualitative visual rating in the specificity cohort was 100%

Safety (preliminary, the NDA is under extensive review):

1. Total 496 subjects in phase I, II and III trials.
2. One SAE, death, during the 48-hr safety monitoring period and unrelated to the drug by the investigator.
3. The most commonly AEs were headache, fatigue and insomnia.

Assessment and plan:

1. Concern of potential misleading by the proposed indication from the sponsor.
   Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of cerebral amyloid deposits.
   Amyvid is not indicated for Alzheimer's disease (AD) screening in patients with no risk factors and not suspected of having the disease.

   Recommend indication: (b) (4)

2. Interpretation of scan results: With Sensitivity of over 90%, negative Amyvid scan makes the presence of cerebral amyloid deposits highly unlikely. Nevertheless, a Negative Predictive Value of Amyvid scan in patients suspected of AD is unknown. With

Specificity of 100%, a positive Amyvid scan confirms the presence of cerebral amyloid and could be supportive in the diagnosis of AD. However it would not provide a definitive diagnosis of AD because other conditions, including normal aging, are also associated with the presence of cerebral amyloid deposits.

3. The long 27 page label (in Microsoft word version) needs significant revision if approval

4. The NDA is under review with the anticipated Priority review timeline.

5. Considering IR: (1) PET imaging of the 35 autopsy patients, (2) discrepancy record of brain tissue evaluation by the neuropathologists

6. The neurology, microbiology, maternal health and DSI clinical inspection review consults on this NDA have been requested.

References:

1. Review Classification Policy: Priority (P) and Standard (S), MAPP 6020.3, CDER, FDA. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082000.pdf

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/s/

QI FENG
02/16/2011

ALEXANDER GOROVETS
02/16/2011

Secondary Clinical Review

Date	11 February 2011
From	Lucie Yang
Subject	Regulatory and Secondary Clinical Review
NDA	202008
Applicant	Avid Radiopharmaceuticals, Inc.
Date of Submission	17 September 2010
PDUFA Goal Date	17 March 2011
Proprietary Name / Established Name	Amyvid / Florbetapir, ^{18}F-AV-45
Dosage and Administration	370 MBq (10 mCi), intravenous
Proposed Indication	PET imaging of β-amyloid aggregates in the brain
Recommendation:	***Complete Response***

I. Introduction

The subject of this secondary review is the New Drug Application (NDA 202008) from Avid Radiopharmaceuticals, Inc. for Amyvid (Florbetapir, ^{18}F-AV-45), a radiopharmaceutical. The product consists of a ligand targeting β-amyloid aggregates that is labeled with the radioactive isotope fluorine-18 (^{18}F). The applicant proposes that Amyvid be used with positron emission tomography (PET) to rule out the presence of β-amyloid in the brain. Individuals with clinical signs and symptoms of cognitive impairment comprise the population of intended use.

The indication statement submitted with the original application reads as follows:

> *"Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical for Positron Emission tomography (PET). Florbetapir F 18 is indicated for PET imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β-amyloid, a defining pathology of Alzheimer's disease (AD)."*

The sponsor subsequently modified the proposed indication statement to the following:

> *"Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β-amyloid in the brain."*

The application includes a single phase 3 trial (A07) enrolling subjects into two cohorts (named "autopsy" and "specificity" by the sponsor) to address two primary endpoints. In this review, the latter cohort will be referred to as the "young, cognitively intact (YCI)" cohort (see section 3 for explanation).

The autopsy cohort (end-of-life) subjects underwent Amyvid PET, and these images were interpreted by three readers on a 5-point scale for amyloid burden; subjects who died within one year underwent autopsy, and histopathology served as the standard of truth (SOT) for a correlation analysis.

Cognitively normal individuals younger than 40 years (the YCI cohort) also underwent Amyvid PET, and a different set of three readers evaluated these images for amyloid burden on a binary scale (+ or -) in order to determine specificity. The negative amyloid status (SOT) of the YCI subjects was presumed based on age, history and genetic testing.

This review will mainly concentrate on efficacy issues in the context of a risk / benefit assessment. Particular attention will be paid to establishing validity and reproducibility of Amyvid PET. The very small number of subjects whose PET images were read using the proposed reading method and who had histopathology as the SOT will be documented. The high degree of inter-reader variability in interpretation of Amyvid PET images will be explored.

The reviewer has examined the relevant excerpts from the NDA and additional submissions by the sponsor, as well as the primary Clinical Review and the Division of Neurology Products consult response.

II. Background / Regulatory Framework

A. Amyvid

Amyvid belongs to a class of drugs termed radiopharmaceuticals in the sense that it comprises of a radionuclide that can be detected *in vivo* and a nonradioactive component that delivers the bound radionuclide to a target in the body. Some radiopharmaceuticals are used for therapy. Amyvid is not intended for therapeutic use. Importantly, as discussed below, amyloid-detecting imaging agents such as Amyvid are not intended to diagnose a disease either. Although regulations for Diagnostic Radiopharmaceuticals may be applied to Amyvid, a more accurate descriptor for amyloid-detecting agents like Amyvid may be "Nontherapeutic Radiopharmaceuticals."

Amyvid targets β-amyloid aggregates which can be found in patients with Alzheimer's Disease (AD) as well as in cognitively normal elderly individuals. Thus, simply detecting amyloid in one's brain does not diagnose AD. Although a clinicobiological lexicon for AD

that does not require pathology has been proposed [1], at this point, definitive diagnosis of Alzheimer's disease requires pathological detection of both amyloid plaques and neurofibrillary tangles. These points were made very clear at the 2008 Advisory Committee (AC) meeting on clinical development of cerebral amyloid-detecting radionuclide imaging products [2].

Some may classify Amyvid as a molecular imaging agent, which is defined by the Society of Nuclear Medicine and the Molecular Imaging Center of Excellence as probes used to visualize, characterize, and measure biological processes in living systems [3]. There are no FDA regulations strictly on the development of molecular imaging agents. However, FDA has published Guidances on developing medical imaging drugs [4-6], and recommendations in these Guidances may be applied to Amyvid.

B. Establishing Effectiveness

According to the Guidance on developing medical imaging drugs [5] and the Code of Federal Regulations (21CFR 315.5), evaluation of a drug's effectiveness entails assessment of the ability to provide useful clinical information related to its proposed indication. Four potential indication categories are: structure delineation; disease or pathology detection; functional, physiological, or biochemical assessment; and diagnostic or therapeutic patient management. A proposed indication can fall into more than one of these categories. According to the CFR, even if an imaging agent's claim does not fall into any of these categories, effectiveness of the imaging agent may still be demonstrated.

As stated above, a positive Amyvid PET test does not constitute a definitive AD diagnosis. Thus, the claim of disease detection will not be applicable to Amyvid, but pathology detection remains a possibility. For each indication category, the CFR describes what the sponsor should demonstrate to make the particular claim. For example, to claim pathology detection for an imaging agent, the sponsor should ideally demonstrate in a defined clinical setting that the drug has sufficient accuracy in identifying or characterizing the pathology.

To establish effectiveness, the Guidance also recommends that the trial demonstrate validity, reproducibility, and clinical usefulness (the latter if not already established) of the imaging agent [5]. Validity is generally evaluated by measuring performance characteristics such as sensitivity and specificity when compared to a standard of truth. In other words, the trial should demonstrate that the agent measures what it purports to measure.

Regarding reproducibility of the test result, this concept refers not only to the use of the drug in an imaging procedure, but also to the interpretation of images obtained with the use of the drug. The sponsor has expressed that Amyvid is intended to be used without incorporating clinical information. Thus, the expectation for reproducibility of Amyvid PET image acquisition and interpretation may be similar to that for certain *in vitro*

diagnostic tests used in hematology or microbiology. Evaluation of reproducibility is particularly important for the Amyvid PET test.

That an imaging agent has clinical utility is important to establish because simply generating an image may not confer benefits to the patient. The clinical utility of some drugs may be self evident or established in the literature. For other agents, a trial may be necessary to demonstrate clinical utility.

C. 2008 Advisory Committee Meeting

Based on criteria for evaluating effectiveness of imaging agents set forth in the CFR and the Guidance, FDA posed questions to an Advisory Committee in 2008 regarding clinical development of radionuclide imaging agents designed to detect cerebral amyloid [7].

The first question the Agency posed to the AC was what clinical utility the detection of cerebral amyloid might have. The Committee's response was that a "negative" amyloid test could have clinical utility in ruling out AD. It was also noted that a "positive" test would have very limited utility because cerebral amyloid can be present in multiple conditions, including normal aging.

The second question FDA posed to the AC was what "standard of truth" (SOT) should be used for phase 3 clinical studies. The consensus decision was that histopathological correlation should be the SOT.

D. Histopathology Methods Used To Establish Standard of Truth

Of the various histopathology techniques for detecting cerebral amyloid, the Bielschowsky silver staining method and immunostaining with a monoclonal antibody to β-amyloid (immunohistochemistry) are the most sensitive methods for showing neuritic plaques (amyloid plus swollen, distorted axons or dendrites) [8].

According to the sponsor, automated immunohistochemistry (IHC) for amyloid is not used clinically on a routine basis due to the need for specialized equipment and training. However, IHC can provide quantitative measures of amyloid burden, with typical values generally not exceeding ~10% area occupied by amyloid.

Routine clinical assessment of amyloid burden using Bielschowsky silver staining can be used to classify neuritic plaque density into 4 categories according to the Consortium to Establish a Registry for AD (CERAD) scoring criteria [9]. These categories are none, sparse, moderate, and frequent. The latter two categories, which can be lumped together and described as "more than sparse," are consistent with AD. In addition to the assessment of amyloid, neurofibrillary tangles must also be taken into account to

determine a likelihood of AD when using the National Institute of Aging (NIA) Reagan Criteria [10].

III.Efficacy

A. Phase 3 Study Design

The sponsor bases the claim of efficacy of Amyvid on the results of a single Phase 3 study (A07) 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.

As recommended by the 2008 AC, histopathology correlation served to address one endpoint. Based on the AC's conclusion that a negative test could have clinical utility for ruling out AD, the sponsor also tested Amyvid PET on subjects presumed to be negative for amyloid to determine specificity as a second endpoint.

The study designs for addressing the two primary endpoints differed in many aspects including the (a) population enrolled, (b) PET image interpretation method, and (c) reference standard for amyloid burden (Table 1).

Study population: The "autopsy" cohort comprised adults with a projected life expectancy of ≤6 months. Even though there were 152 subjects in the autopsy cohort imaged, only 29 subjects were included in the primary efficacy analysis for correlation with histopathology. The "young, cognitively intact cohort" (YCI) comprised adults equal to or younger than 40 years without risk factors for AD. The sponsor refers to this cohort as the "specificity cohort." This term will not be used in this review because the young, cognitively intact subjects are not part of the intended use population; "specificity" describes how often a test is negative only in the population of intended use for whom the target condition is absent. 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 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 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.

Table 1. Comparison of study designs for the two endpoints in trial A07

	"Autopsy" cohort	**"Young, cognitively intact" (YCI) cohort**
Population	adults with life expectancy ≤ 6 months and various levels of cognitive status 152 subjects enrolled	cognitively and neurologically healthy adults ≤ 40 years without risk factors for AD 74 subjects enrolled
Size of primary efficacy population	n=29 died within 1 year of PET imaging mean age 80.0	n=47 no genetic risk factor for AD [ApoE ε4 negative] mean age 26.3
PET image interpretation method	5-point scale (0-4)	binary scale (+ or -)
Reference standard for amyloid burden	histopathology of subjects who died within 1 year of PET imaging specifically, quantitative immunohistochemistry (IHC) indicating % area occupied by amyloid	negative amyloid status presumed
Primary endpoint / win criteria	statistically significant correlation (Spearman's $\rho > 0$, $p \leq 0.05$)	specificity ≥ 90% (95% CI: 80-98%)

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-

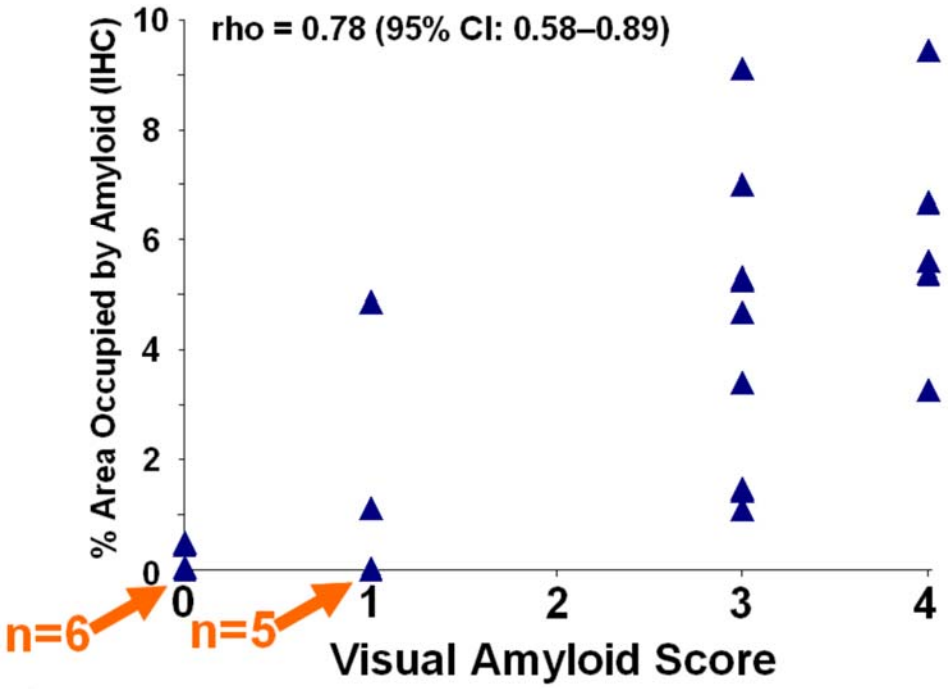
quantitative visual rating scale (0-4) for Amyvid PET images (median of 3 independent readers) and (b) the cortical amyloid burden by pathology using quantitative IHC. Achieving success required a statistically significant correlation (Spearman's $\rho>0$, $p\leq0.05$). For the YCI cohort, the primary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

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.

B. A07 Results: Autopsy Cohort

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 $\rho=0.78$, $p<0.0001$ (Figure 1). Thus, the primary endpoint was met for the autopsy cohort.

Figure 1. Autopsy Cohort Primary Efficacy Result.



Although the correlation is statistically significant, close examination of Figure 1 reveals that there is not an exact match between the amyloid levels established through reads of the PET images and levels determined by histopathology. For example, a median amyloid rating of 3 by the three PET readers could represent from ~1% to ~7% area occupied by amyloid. This result could in part be explained by how the PET readers were trained: Figure 2, an excerpt from the slides used to train blinded readers in A07, illustrates that the PET image readers were informed that moderate amounts of amyloid corresponding to a rating of 2 on the 5-point scale will be rare.

Figure 2. Excerpt from Slides used for Blinded Reader Training in Trial A07

- The most important decision you will make:
  Is the patient mainly positive (3/4) or mainly negative (0/1)?
  In prior studies most subjects are either 0/1 or 3/4. It's rare to have only moderate amounts of amyloid (2).

C. A07 Results: YCI Cohort

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, the lack of gross atrophy on the PET images for YCI subjects likely biased the results in favor of high specificity because of the difference in degree of atrophy between subjects on the two extremes (YCI with mean age of 26 years versus end-of-life with mean age of 79 years).

D. Critique of A07 Efficacy Data

In addition to the concerns stated above, the reviewer will discuss limitations of trial A07 related to study design, sample size, and inter-reader variability.

1. Study design: Given that the 2008 AC concluded that a negative amyloid test could have clinical utility in ruling out AD, demonstrating that sensitivity is at a clinically relevant level is particularly important. Being certain that a negative result is truly a negative would give a clinician confidence that the differential diagnosis could be directed toward causes of memory impairment or cognitive decline other than AD. Demonstrating a high specificity is also important, but less so than a high sensitivity

because a positive test does not definitively rule in or out any particular diagnosis. That specificity was measured in subjects outside of the population of intended use in A07 further reduces the clinical relevance of the high specificity result.

A limitation of study A07 is that sensitivity was not an endpoint and success criteria for sensitivity was not prespecified. By adding autopsy cohort subjects presumed positive for amyloid (based on the median rating by the three readers for the autopsy cohort) into the image pool of the YCI subjects, the sponsor could calculate "sensitivity" in an exploratory manner. Importantly, the truth standard was not histopathology for 26 of these 40 subjects (which is why "sensitivity" used here will be in quotes). Using the majority read of 3 readers, "sensitivity" was reported to be 95%. Analysis by reader reveals point estimates for "sensitivity" of 85%, 93% and 95%. The caveat of being able to visualize gross brain atrophy on PET images could also bias in favor of high sensitivity here because the advanced ages of these 40 subjects predispose them to atrophy that is likely absent in the YCI subjects.

Sensitivity can also be calculated using autopsy cohort data by transforming the semi-quantitative scale for amyloid burden on PET images into a binary scale. The sponsor defined a post-hoc threshold for amyloid burden on PET images as follows: 0-1 = amyloid absence, 2-4 = amyloid presence. For IHC results, the sponsor defined <1% as amyloid absence and >1% as amyloid presence based on comparison with the NIA-Reagan criteria for AD likelihood. Using these thresholds, sensitivity of the median PET read was 85% using IHC as the truth standard. *However, sensitivity for one of the three readers was as low as 55%* (85% and 90% for the other two readers), calling into question the validity and reproducibility of Amyvid PET. Inter-reader variability will be explored further below.

The subjects included in A07 are not representative of the intended use population. Thus, any estimates of performance characteristics are subject to spectrum bias. That being said, the 2008 AC's recommendation that histopathology should be the standard of truth raises feasibility issues for studying subjects presenting with memory impairment or cognitive decline.

2. <u>Sample size:</u> The applicant's proposed reading method for routine clinical use of Amyvid PET is on a binary scale (+ or – for amyloid). According to the 2008 AC, the standard of truth for a Phase 3 study of an agent designed to detect amyloid should be histopathology. *A very significant limitation of this NDA is that PET images from only 14 subjects with histopathology data were read using the proposed reading method.* With this very small sample size (all positive for amyloid), the validity and reproducibility of Amyvid PET cannot be convincingly demonstrated. For a confirmatory study, demonstration of high performance characteristics achieved by at least three readers interpreting PET images using the method proposed for routine clinical use in a much larger number of subjects would have been helpful.

3. Inter-reader variability: Another concern is that readers trained in the same manner did not necessarily produce similar interpretations for a given Amyvid PET image. Based on a detailed analysis of the rating assigned by each reader to the PET images and on performance characteristics for each reader, the Clinical Review describes the undercalling and overcalling by two readers for the autopsy cohort with respect to IHC. Only one of the autopsy cohort readers appeared to achieve both high sensitivity and specificity; according to the sponsor, this reader had previous experience assessing amyloid burden using a different imaging agent. The observations reported below regarding inter-reader variability are based on the Neurology consult response and complement those described in the Clinical Review.

   For the primary efficacy population in the autopsy cohort, the images for only 17% of the subjects (5 of 29) were rated identically by all three readers on the 5-point scale. Applying the sponsor's post-hoc thresholds for amyloid presence or absence on PET images as described above in section III.D.1. (0 or 1 as negative), in nearly ¼ of the subjects (7 of 29, 24%), at least one reader would have had a different binary interpretation of amyloid status from the other two readers (difference between highest and lowest rating ≥2, and lowest rating either 0 or 1). Differences between the highest and lowest rating for PET images from the autopsy cohort are summarized in Table 2. Using histopathology as the truth standard, at least one reader would have interpreted the PET image incorrectly for 31% of subjects (9 of 29).

Table 2. Autopsy cohort rating differences among 3 readers

	Difference between highest and lowest rating among 3 readers (5-point scale from 0-4)		
	2	3	4
Primary efficacy population n=29	21% (n=6)	7% (n=2)	0% (n=0)
All subjects with ratings n=147	14% (n=21)	18% (n=27)	2% (n=3)

   If all the PET images from autopsy cohort subjects (including those who did not die within 1 year of the PET imaging) were considered in a similar analysis, the images for only 25% of the subjects (37 of 147) were rated identically by all three readers on the 5-point scale. *Strikingly, in over 1/3 of the subjects (50 of 147, 34%), at least one reader would have had a different binary interpretation of amyloid status from the other two readers. Truly concerning is the observation that there were 3 of 147 subjects in which at least one reader rated the PET image as 0 (no amyloid) and at least one other reader read the same scan as a 4 (highest amyloid). For 9 of 147 subjects, at least 1 reader rated the scan as 0 for amyloid and at least one other reader rated the PET image as a 3 on a 0-4 scale.*

For the 40 autopsy cohort subjects whose images were added to the image pool of the YCI cohort, consistency in amyloid burden interpretations can be assessed across all 6 readers by transforming the 0-4 ratings by 3 readers onto the binary scale using the sponsor's post-hoc threshold. It is very concerning that for 45% of subjects (18 of 40), 1 reader differed from the other 5 readers regarding amyloid presence or absence. For 10% of subjects (4 of 40), 2 readers differed from the other 4 readers regarding amyloid presence or absence. In 5 of 40 subjects (12.5%), 1 of the 3 readers who read on a binary scale interpreted amyloid presence or absence differently from the other two readers.

Similarly, for the PET images of the 74 subjects in the YCI cohort (regardless of ApoE ε4 status), 1 reader came to a different conclusion regarding amyloid presence or absence from the other 2 readers for 11% of subjects (8 of 74).

With the variability in interpretation of Amyvid PET images described above, reproducibility and clinical utility of Amyvid PET are severely challenged.

E. Phase 1 Study A04: Test-retest Reproducibility of Amyvid PET

A Phase 1 trial was designed to assess test-retest reproducibility of Amyvid PET in cognitively normal volunteers and probable AD patients. Each subject underwent Amyvid PET imaging on 2 separate days separated by a maximum of 4 weeks. Images were read by one reader blinded to clinical information and to whether the image was a test or retest image. The single blinded reader classified images as amyloid positive or negative. Of the ten probable AD patients, the test and retest image of 1 subject was read differently (kappa 0.74). Of ten cognitively normal subjects, all test and retest images were read identically. The results of this study suggest that variability in image acquisition and display may not be significant, but the sample size was extremely small. Of note, the only difference in the interpretation of test versus retest image occurred in a probable AD subject, so it is possible that subtle differences in image acquisition or display may make a difference in determination of amyloid presence / absence for individuals who may not be cognitively intact.

F. Phase 2 Study A05: Amyvid Efficacy and Safety in Older Healthy Volunteers, Mild Cognitive Impairment (MCI) Patients, and Alzheimer's Disease Patients

The objectives of a Phase 2 study included determination of the prevalence of amyloid positivity based on Amyvid PET in subjects with mild cognitive impairment (MCI). All 184 subjects were over 50 years of age (79 cognitively normal subjects, 60 MCI subjects, 45 AD subjects). Each subject underwent an Amyvid PET scan. Images were read by three readers blinded to clinical information using a semi-quantitative scale and a binary scale. Only the results using the binary scale are depicted in

Table 3. Phase 2 Study A05 Results Using Binary Read (Majority Rating)

Amyloid	HC n=78	MCI n=60	AD n=45
Positive	11 (14%)	23 (38%)	34 (76%)
Negative	67 (86%)	37 (62%)	11 (24%)

Importantly, patients who may have intermediate levels of brain amyloid were imaged using Amyvid. Thus, this study is notable for enrolling subjects who are likely in the population of intended use for Amyvid. Study A05 lacked a truth standard, so the reliability of the imaging results cannot be confirmed.

G. Summary Remarks Regarding Amyvid Efficacy Data

In conclusion, the two primary endpoints in the single Phase 3 trial were met. Study A07 is commendable for successfully employing histopathology as a standard of truth. The statistically significant correlation provides some evidence of acceptable validity.

However, significant limitations in study design, sample size, and inter-reader variability cast doubt on Amyvid PET validity, reproducibility, and clinical utility. The most significant, yet rectifiable, limitation is that only 14 subjects with histopathology data had their PET images read using the proposed interpretation method for routine clinical use. The available data suggest that there is variability in Amyvid PET image interpretation.

This reviewer supports the opinion of the primary clinical reviewer that the efficacy data in this NDA fails to provide convincing evidence to support the efficacy of Amyvid PET for imaging β-amyloid aggregates in the brain.

IV. Safety

According to the sponsor, no safety signals have emerged for Amyvid throughout clinical trials. The applicant states that 496 subjects have been exposed to Amyvid.

V. Advisory Committee Meeting

This application was discussed at a Peripheral and Central Nervous System Drug Advisory Committee on January 20, 2011 where the consensus (and vote) found the data submitted to the NDA insufficient to support a marketing approval recommendation. The concerns included inconsistency in the PET scan readings, inadequate data for validating the binary read method as compared to a truth standard,

absence of an established clinically-applicable reader training program, and the need to validate the reader training program on reading PET images of the population of intended use.

VI. Pediatrics

Amyvid is a new molecular entity so pediatric studies have to be considered under the Pediatric Research and Equity Act. The applicant has requested a full waiver of such studies. The Pediatric and Maternal Health Staff (PMHS) agrees with this reviewer and with the applicant that the waiver is appropriate.

VII. Other Relevant Regulatory Issues

The Office of Compliance recommends withholding approval. At the time this review is written, no further details are available.

The Division of Scientific Investigations conducted three good clinical practice (GCP) inspections (applicant and two clinical sites identified by the clinical reviewer). No major deficiencies were observed.

VIII. Labeling

No systematic labeling review has been performed so far in this review cycle. When approval of this application is being considered, particular attention will be paid to incorporating instructions on reader training. In addition, careful consideration will be given to the addition of "limitations of use" and to the removal of the word "diagnostic" in the indication statement.

IX. Recommendations / Risk Benefit Assessment

A. Recommended Regulatory Action

The secondary clinical reviewer recommends against approving the New Drug Application 202008 for Florbetapir, 18-F AV-45 (Amyvid).

B. Risk Benefit Assessment

Although no significant risks associated with the use of Amyvid have been identified, no convincing evidence of benefit from Amyvid PET has been demonstrated either. The submitted data fail to confirm the efficacy of Amyvid for imaging β-amyloid in the brain. The inconsistency between the interpretations of amyloid presence or absence by different readers using the same images (and potential variability in image display as well) is particularly concerning. The lack of apparent benefit is accentuated by the extremely small sample size of 14 with histopathology and PET images read using the proposed interpretation method for routine clinical use. Given that clinical benefit may be conferred only by a negative test, sensitivity with pre-specified success criteria will be particularly important to assess.

C. Recommendations For Addressing Deficiencies

In conclusion, additional clinical trial data will be required to adequately demonstrate benefit for the use of Amyvid with PET. The following draft comments to the applicant provide rationale for not approving the product and lists the requests and recommendations for addressing the identified deficiencies.

REGULATORY

1. Note: This deficiency will need to be described once the full compliance report is completed.

CLINICAL

2. The supplied clinical data in the original NDA submission did not provide substantial evidence of Amyvid efficacy. This conclusion was also the general opinion expressed at the January 20, 2011 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. A clinically-applicable reader training program has not been established and validated for a clinically meaningful population. Furthermore, there is insufficient data to validate the binary read method as compared to histopathology.

3. You have indicated that you intend for readers to interpret Amyvid PET images on a binary scale (positive or negative for amyloid). If this continues to be your intention, we recommend that you design a clinically-applicable reader training program for binary interpretation. Once established, this training program will need to be tested on at least three readers in order to verify the effectiveness of the training. We reiterate that the training program that is tested should be the very same training program that you anticipate any potential Amyvid PET image reader to use in the future. Of particular importance is the degree of human interaction required to provide feedback on correct and incorrect image interpretations for test cases and the underlying rationale.

4. The testing of the reader training program will require training of at least three readers using the established clinically-applicable reader training program. Once trained, readers will interpret the following randomized images from Study A07 and Study A05: all 152 autopsy cohort subjects from Study A07 and 184 subjects from Study A05 (total 336 subjects). Study A05 includes subjects in the intended population for Amyvid. The autopsy cohort from Study A07 includes all individuals with histopathology; those who do not have histopathology are in age groups which may have a similar degree of atrophy as the intended population. Furthermore, these subjects have baseline diagnosis (AD, MCI, healthy) information.

5. We request that you make use of the histopathology results from subjects who have died in year 2 after enrollment in your Study A16 conducted in Europe, which is a continuation of the autopsy cohort from Study A07.

6. Pre-specified success criteria for sensitivity and specificity would be expected, with threshold values of 70% and 80%, respectively. Success criteria for inter-reader reproducibility should also be pre-specified.

7. During the development of subsequent studies, we encourage you to consider (a) which histopathology method (INC vs CERAD) to use as the truth standard (for those who undergo autopsy) and (b) what threshold to use for distinguishing positive from negative amyloid burden. Factors to consider include reproducibility of the histopathology result and clinical appropriateness. Your choice of standard of truth (IHC versus modified CERAD) may be reflected in the label if Amyvid is marketed.

8. You may wish to develop alternative approaches to obtaining persuasive clinical evidence of your product's efficacy. We encourage you to request a meeting to discuss these plans prior to the initiation of new clinical studies.

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/s/

LUCIE L YANG
02/12/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202-008
Priority or Standard	Priority
Submit Date(s)	September 17, 2010
Received Date(s)	September 17, 2010
PDUFA Goal Date	March 17, 2011
Reviewer Name(s)	Qi Feng, MD, PhD
Review Completion Date	February 4, 2011
Established Name	Florbetapir, 18-F AV-45
(Proposed) Trade Name	Amyvid, Eli Lilly & Company
Therapeutic Class	Diagnostic molecular imaging agent
Applicant	Avid Radiopharmaceuticals, Inc.
Formulation(s)	370 MBq (10 mCi) florbetapir F 18 in 10% (v/v) ethanol, 0.45% (w/v) sodium ascorbate, 0.81% (w/v) sodium chloride sterile aqueous solution, at a strength of 37-1900 MBq/mL (1-50 mCi/mL) per unit dose vial or syringe at the time of calibration.
Dosing Regimen	370 MBq (10 mCi)
(Proposed) Indication(s)	*"Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β-amyloid in the brain."* (as proposed on 11/23/2010)
Intended Population(s)	Adult patients with cognitive dysfunction

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Abbreviations and Definition of Terms

AD: Alzheimer's disease
AE: adverse event/adverse experience
ApoE: Apolipoprotein E
CERAD: Consortium to Establish a Registry for Alzheimer's Disease
CFR: Code of Federal Regulation
CI: confidence interval
CMC: Chemistry Manufacturing and Controls
CT: computed tomography
F-18: fluorine-18
F-19: fluorine-19
FDG: fluorodeoxyglucose (F-18)
g: gram
GCP: Good Clinical Practice
IHC: immunohistochemistry
IND: Investigational New Drug
IV: intravenous
HC: healthy control
KeV: kilo-electron volt
MBq: megabecquerel
mCi: millicurie
MCI: mild congnitive impairment
mg: milligram
MHD: maximum human dose
mL: milliliter
MRI: magnetic resonance imaging
mSv: millisievert
NDA: New Drug Application
NOAEL: no observable adverse effect level
NPV negative predictive value
PET: positron emission tomography
PiB: Pittsburgh compound B
PPV positive predictive value
rho: Spearman's rank correlation coefficient
SAE: serious adverse event
SOT: standard of truth
SUV: standard uptake value
SUVR standard uptake value ratio
TEAE: treatment-emergent adverse event
µg: microgram

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to FDA guidelines on regulatory expectations for diagnostic radiopharmaceutical agents, phase 3 clinical trial data should demonstrate clinical utility (if not already established), test validity and reproducibility [1, 2] in order for an imaging agent to be approved. Based on these criteria and the review findings, the clinical reviewer does not recommend approval of NDA 202-008 for Amyvid (Florbetapir F-18 Injection) for the proposed indication of amyloid detection in the brain with a PET scan. This recommendation is based on review of the efficacy data from the NDA submission, mainly from the single pivotal phase 3 clinical trial for 18-F-AV-A07 (A07) and the phase 2 trial for 18-F-AV-A05 (A05). The recommendation is not based upon the submitted safety data.

At this time, the reviewer recommends that the sponsor

1. generate and submit a clinical image reader training program to ensure accurate and reproducible imaging interpretation for the clinicians.
2. design and conduct the following study in order to demonstrate validity and reproducibility of Amyvid PET:
   Re-read the PET images from autopsy and specificity cohorts of A07 and healthy control with normal cognitive function, mild cognitive impairment (MCI) and Alzheimer's disease (AD) subjects of A05 trials by three new independent readers with a single review charter using the proposed visual interpretation method on a binary scale (positive or negative) in order to validate performance characteristics, and to assess inter-reader variability and reproducibility of Amyvid PET.

1.2 Risk Benefit Assessment

To date, Amyvid does not have an acceptable risk benefit assessment. Rationale is as follows:

1. Small sample size (n = 14) to validate the proposed image interpretation methodology in subjects with amyloid status confirmed by histopathology.

2. Pending submission of a clinical image reader training program.

3. High inter-reader variability for PET image assessment among the three blinded readers in the autopsy cohort.

4. The inter-reader reproducibility among subjects with intermediate levels of amyloid in the brain, potential target MCI population, is unknown.

5. Phase 3 trial subjects were not the population of intended use. If marketed, Amyvid would likely have a relatively broad target patient population (adults with cognitive deficit) in the real world, and these subjects were not tested in the Phase 3 trial.

6. Wide range of true amyloid burden by immunohistochemistry for some PET ratings (median of three readers) of amyloid status.

1.3 Recommendations for Postmarket Risk Management Activities

None at the present time

1.4 Recommendations for Postmarket Studies/Clinical Trials

Pending

2 Introduction and Regulatory Background

Pending

2.1 Product Information

Alzheimer's disease (AD) is the most common form of dementia in individuals over 65 years of age. In the early stages, the most commonly recognized symptom is inability to acquire new memories, such as difficulty in recalling recently observed facts. When AD is suspected, the

diagnosis is usually confirmed with behavioral assessments and cognitive tests. As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long-term memory loss, and general withdrawal of the sufferer as his/her senses decline. According to the Alzheimer's Association's "2009 AD Facts and Figures," 5.3 million Americans are living with AD [3].

The definition of Alzheimer's disease is undergoing evolution. Although a clinicobiological lexicon for AD has been proposed, at this time, AD can only be definitively diagnosed by post-mortem pathology. Clinically, AD is usually diagnosed as “probable AD” or “possible AD” based on the presence of characteristic neurological and neuropsychological features (cognitive dysfunction, dementia), patient history, family history, and the absence of alternative conditions. Multiple studies have showed that clinical diagnosis is imperfect, with approximately 81% sensitivity (range 49% to 100%) and 70% specificity (range 47% to 100%) when the gold standard is pathology at autopsy [4]. Currently, imaging modalities such as CT, MRI and FDG PET/CT are primarily used to help exclude other cerebral pathology or subtypes of dementia. To date, there is no approved treatment or medication which consistently delays or reverses AD progression after diagnosis.

The risk factors for AD include age (> 65 yrs old), heredity (first degree relatives, parents, sister and brothers), sex (female more likely), mild cognitive impairment, lifestyle (hypertension, hypercholesteremia and diabetes), and less education. One genetic risk factor is apolipoprotein E (ApoE) ε4 on chromosome 19, which occurs in about 40% of all individuals who develop late-onset AD.

The exact cause and progression of AD are not well understood yet. Research suggests that the disease is associated with plaques (primarily composed of beta amyloid peptides) and neurofibrillary tangles in the brain. The AD pathology diagnosis requires presence of both amyloid plaques and neurofibrillary tangles.

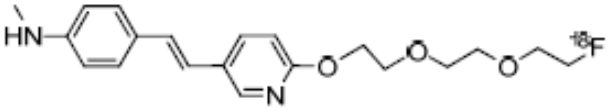
Amyloid consists of insoluble fibrous protein aggregates. Abnormal accumulation of amyloid in organs may lead to amyloidosis or play a role in various neurodegenerative diseases, including AD, Parkinson's disease, transmissible spongiform encephalopathy, Huntington's disease, familial amyloid polyneuropathy and cerebral amyloid angiopathy [5, 6, 7, 8, 9].

Pittsburgh compound B (PiB), a fluorescent analog of thioflavin T, can bind beta-amyloid plaque in post-mortem brain tissue in *in vitro* studies, suggesting the potential for use as a PET tracer for amyloid detection in the brain [10].

Amyvid is a radiopharmaceutical tracer and the non radioactive ingredient of the drug is an analog of PiB. The radioactive isotope of the drug is fluorine-18, which decays by positron emission with a half-life of 110 minutes.

Amyvid comprises of 370 MBq (10 mCi) florbetapir F-18 in 10% (v/v) ethanol, 0.45% (w/v) sodium ascorbate, 0.81% (w/v) sodium chloride sterile aqueous solution, at a strength of 37 - 1900 MBq/mL (1 - 50 mCi/mL) per unit dose vial or syringe at the time of calibration.

The chemical name of Amyvid is (*E)-4-(2-(6-(2-(2-(2- [18F]fluoroethoxy)ethoxy)ethoxy) pyridin-3-yl)vinyl)-N-methylaniline* which has the following structure:



The molecular formula of the drug is $C_{20}H_{25}[18\text{-}F]N_2O_3$ and its molecular mass is 359 atomic mass unit.

On October 23, 2008, FDA convened a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee (AC) to discuss strategies for clinical development of PET tracers designed to detect amyloid. One question posed by FDA was, "*To what extent, if any, would an indication for the use of an in vivo diagnostic radiopharmaceutical agent for the "detection of cerebral amyloid" provide useful clinical information?"* The committee agreed that a negative amyloid test could have clinical utility in ruling out a diagnosis of AD. Additionally, the

committee noted that a positive test would only be supportive in the diagnosis of AD and would not provide a definitive diagnosis. A second question posed by FDA was, "*If an in vivo diagnostic radiopharmaceutical is clinically useful in the "detection of cerebral amyloid," what should be a "standard of truth" in phase 3 clinical studies?* " Here the committee overwhelmingly agreed that histopathological correlation should be the "standard of truth" in phase 3 clinical studies [11]. The crux of the Amyvid NDA is a Phase 3 histopathological correlation, and this data is the main focus of the NDA review.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there is no approved imaging agent in the United States for detection of amyloid in the brain.

2.3 Availability of Proposed Active Ingredient in the United States

Amyvid is a new molecular entity and it is not currently marketed in the United States.

If approved, Amyvid will be manufactured by Avid Radiopharmaceuticals Inc. at multiple facility sites. The drug is a conjugate of the Florbetapir F-19 molecule (19-F is the stable isotope of element fluorine), with radioisotope 18-F replacing 19-F in the conjugation process. The final precursor, Florbetapir 19-F, is manufactured by Girindus America, Inc., 8560 Reading Road, Cincinnati, OH 45215, USA. The manufacturing of Amyvid (Florbetapir 18-F) is performed by 19 facility sites of Cardinal Health, Inc (8) and PETNET Solutions (11) throughout the United States. All starting materials, reagents, solvents and other materials used for the manufacturing of the drug are controlled and released according to Avid specifications prior to use.

2.4 Important Safety Issues with Consideration to Related Drugs

Amyvid is a compound with the radioactive isotope fluorine 18 (F-18). Radiation safety concerns are present secondary to positron emission of gamma radiation (photon energy of 511 KeV) by the F-18 radioisotope. The reported effective dose of 7.03 mSv for a 10 mCi dose of Amyvid represents an acceptable level of radiation exposure to the human subject given that guidelines for radiation workers recommend a maximum exposure limit of 50 mSv per year [12].

A 10 mCi Amyvid dose is in the lower range of radiation effective dose for general nuclear medicine imaging procedures.

It is not known whether Amyvid is excreted into human milk. Therefore, a decision regarding the duration for which to interrupt nursing (generally at least 5 times the half-life of the specific radioisotope in order to minimize risks to nursing infants) following drug administration should be made by the patient's physician.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

The regulatory history of the NDA:

1. 01/08/2007: Exploratory IND 76-852 was filed and withdrawn on 02/14/2008
2. 03/06/2008: Pre-IND and then IND 79-511 was filed
3. 10/23/2008: Advisory Committee (AC) Meeting held to discuss clinical development of PET tracers for the detection of amyloid
4. 11/03/2008: Type-C meeting to reiterate AC recommendations regarding the use of histopathology as the standard of truth
5. 02/11/2009: Type-C meeting to discuss "autopsy" and "specificity" cohorts proposed for the phase 3 trial
6. 04/13/2010: Reproductive toxicology waiver was requested by the sponsor
7. 07/26/2010: Carcinogenicity testing waiver was requested
8. 03/09/2010: Pediatric testing waiver was requested
9. 06/17/2010: Priority review was requested
10. 07/19/2010: Type-B Pre-NDA meeting
11. 09/17/2010: Submission of NDA 202-008 Amyvid
12. 10/07/2010: Sponsor presented NDA to FDA review division
13. 11/15/2010: Sponsor's second presentation of NDA to FDA review division
14. 11/23/2010: Type-B meeting during which the sponsor specified that a binary (positive/negative amyloid) image interpretation methodology was the intended reading method for Amyvid PET images in clinical practice. Sponsor proposed a new indication and label.

15. 01/20/2011: AC Meeting held to discuss the new drug application (NDA) 202-008, Amyvid, Florbetapir F 18 Injection.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

To date, the data quality and integrity of the phase 1, 2 and 3 trials submitted appear acceptable according to regulatory expectations.

The Division has consulted the Division of Scientific Investigations (DSI), Center for Drug Evaluation and Research, FDA regarding site inspections for the NDA. Study sites were selected for inspection based upon the following reasons:

1. The study was considered as the most important for efficacy and safety claims (A07).
2. The number of subject enrolled at the sites exceeded the average number of patients enrolled in the study.
3. The sites with more protocol deviations compared to other sites.

Table 1. Description of Study Sites for DSI Inspections

	Site Name and Address	Trial Name	Subject # (n)	Indication
1	Site #145, Banner Alzheimer's Institute, 901 East Willetta St., Phoenix, AZ 85006	A07	20	3 autopsies, 11 protocol violations and 2 TEAE
2	Site #217, Duke University, PET facility, Room 0402, Yellow Zone, Duke South, Campus Box 3949, Durham, NC 27710	A07	25	4 autopsies, 1 protocol violations and 4 TEAE

TEAE = treatment-emergent adverse event

The overall assessment of findings and general recommendations from the DSI site inspection preliminary report indicated that as part of the PDUFA-related inspections two U.S. clinical

investigator sites and Sponsor were inspected in support of this application, for Protocol 18F-AV-A07. The inspection documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations, and the data are considered reliable in support of the application.

3.2 Compliance with Good Clinical Practices

Based on the sponsor's statement at the beginning of each individual clinical report, the studies were conducted in full accordance with the Declaration of Helsinki; the International Conference on Harmonization (ICH) consolidated guideline E6 - Good Clinical Practice (GCP) and any applicable national and local laws and regulations.

3.3 Financial Disclosures

According to the submission, the A07 study was conducted at 34 study centers in the United States, 25 of which enrolled at least 1 subject (range from 1 - 25 subjects). Principal investigators at these 25 sites had financial disclosures in the submission.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Controls (CMC) review is pending. At this time, no issues that might affect efficacy or safety have been reported.

4.2 Clinical Microbiology

No issues to report at this time.

4.3 Preclinical Pharmacology/Toxicology

In vitro binding studies showed high amyloid binding affinity of Amyvid to amyloid without significant cross reactions to the prevalent central nervous system (CNS), peripheral nervous system (PNS) or cardiovascular receptors. No adverse effects of the non-radioactive form of the

drug on the CNS were observed in the standard functional observational battery test up to 100X the intended maximum human dose (MHD) in rats.

An acute dose study was conducted in rats, and the NOAEL (no observable adverse effect level) was determined to be at least 100 times MHD. The potential toxicity of 28 days of repeated IV injections of the drug was tested in rats and Beagle dogs, and the NOAEL was found to be at least 25x the MHD.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Amyvid binds to amyloid plaques in human brain tissue obtained post-mortem from subjects with AD pathology. In equilibrium binding studies using homogenates of AD brain tissue, the dissociation constant for florbetapir was measured at K_d = 3.7 nM. The binding was visualized in brain sections from subjects with AD pathology with autoradiographic methods. Positive staining was observed in gray matter of post-mortem AD brains, but not in control tissue from subjects without AD pathology. Amyloid deposition was assessed using neuropathological staining procedures, including Bielschowsky silver staining and immunohistochemistry with anti-amyloid antibodies. *In vitro* studies demonstrated correlations between drug binding and amyloid deposition.

4.4.2 Pharmacodynamics

The radioactive imaging signals generated by Amyvid, which can be measured by standard uptake value (SUV), were visible from 30 to 90 minutes postdose. The images from 30 - 40 minutes and 50 - 60 minutes postdose showed good agreement by the blinded readers, suggesting the window of time for imaging after tracer injection.

The test-retest reproducibility study (A04) result showed good intra-class correlation and low test-retest variability. A comparison of a 10 minute versus a 20 minute scan acquisition period

showed no difference in radioactive signals. Therefore, a 10 minute PET scan is recommended for the imaging for reasons of patient comfort and compliance.

4.4.3 Pharmacokinetics

Amyvid bio-distribution study A02 showed that the drug was rapidly distributed throughout the body following IV administration. Rapid clearance from circulation and localization in the liver/gastrointestinal system was observed. Images over time show that elimination occurs primarily by way of clearance through the liver and excretion into the gallbladder and the intestines. Some accumulation/excretion is also observed in the urinary bladder. The drug is very rapidly cleared from circulation postdose. Less than 5% of the injected radioactivity remains in blood by 20 minutes following administration.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 summarizes all studies submitted in the NDA:

Table 2. All Studies Submitted in the NDA

Phase	Study ID	Subjects # (n)	Objectives
1	A01	32	PK
	A02	9	Dosimetry
	A03	20	Dose (3 vs. 10 mCi)
	A04	25	Test-retest
	A06	41 (re-read of select A01 and A03 images)	Timing for imaging
2	A05	184	Imaging profile, safety
3	A07	226	PET-pathology correlation, specificity
		Total 496	

5.2 Review Strategy

The clinical reviewer will verify, evaluate and analyze all data submitted related to the efficacy and safety claims of Amyvid. There were seven studies in total, including five phase 1 studies, one phase 2 study, and one phase 3 study. Because there is only one pivotal phase 3 trial (A07)

and this was the only trial in which histopathology was used as the standard of truth (SOT), ─ as requested by 2008 AC members ─ the reviewer will primarily and extensively concentrate on this trial. The review includes detailed data verification, dissection and analysis of the primary and secondary endpoint data, as well as critiques of the weaknesses in trial design, data and conclusions claimed. For the drug safety review, the reviewer will assess data from all 7 trials submitted in the NDA. A total of 496 subjects received at least 1 dosing of the drug.

For efficacy, the clinical review assesses the sponsor's results using Spearman's rank correlation coefficient (rho), sensitivity, specificity, positive predict value (PPV), negative predictive value (NPV) and accuracy. The lead statistical reviewer, Dr. Lan Huang, has been actively involved in raw data verification and analysis.

6 Review of Efficacy

6.1 Indication

In the original NDA submission, the proposed indication was:

> "*Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β-amyloid, a defining pathology of Alzheimer's disease (AD)"*

After several discussions with the FDA, the sponsor has revised the proposed indication to:

> "*Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of β-amyloid in the brain."*

Reviewer comments: "*……significant levels of β-amyloid in the brain*" might be misleading or not be specific enough. It might be necessary to add "**(more than sparse neuritic plaques by the CERAD rating)"** after the "*……significant levels of β-amyloid in the brain*" to more precisely specify the amyloid level detected so that clinicians may have a better understanding of what a negative Amyvid PET scan suggests.

6.2 Efficacy Summary

The Amyvid efficacy results are mainly from the "autopsy" and "specificity" cohorts of trial A07.

1. In the only Phase 3 trial for this NDA (A07), only 14 subjects had (a) PET images read using the sponsor's proposed reading method for routine clinical use (positive or negative for amyloid) and (b) histopathology as a standard of truth. This small sample size is a significant limitation of this NDA.

   Three different visual rating methods were used to evaluate amyloid burden on PET images in the A07 trial. First, a 5-point scale (0 - 4) was used for the autopsy cohort. Second, a binary rating scale (positive or negative) was used for PET images of the young, cognitively normal subjects (and the 40 autopsy cohort subjects added to reduce bias). Both of these scales were applied to estimate amyloid burden in gray matter across the whole brain (global). A third visual rating method (3-point scale from 0 - 2) was used to evaluate the amyloid burden in each of 6 regions of the brain (regional); according to the sponsor, this information was not used in any analysis. In a meeting on 11/23/2010, the sponsor informed FDA that the intended reading method for routine clinical use of Amyvid PET scans is a binary (positive or negative) scale. As stated above, PET images from only 14 subjects who had histopathological confirmation of amyloid status were read using this binary scale.

   PET images read on the 5-point was converted to a binary scale on a post-hoc basis by the sponsor to calculate performance characteristics (sensitivity, specificity).

Importantly, the thresholds for designating a PET scan as positive or negative based on the 5-point scale were not prespecified and prospectively tested.

2. For the autopsy cohort, the sponsor reports a statistically significant Spearman's correlation (rho = 0.78, $p < 0.0001$) between the median semi-quantitative 5-point visual rating of the PET image by three blinded readers and the percent cortical gray matter area occupied by amyloid assessed using quantitative IHC. Therefore, the primary endpoint for this cohort was met. However, detailed analysis of individual reader rating of amyloid burden on PET images demonstrates that the median rating obscures the high inter-reader variability among the 3 readers. This observation suggests low reproducibility of visual rating across readers. In addition, there is a wide range of true amyloid burden by IHC for some median PET ratings.

3. For the cohort of young, cognitively normal subjects without known genetic risk factors for AD (termed "specificity cohort" by the sponsor), high specificity (100%) of the majority read by three readers blinded to clinical information was demonstrated. Importantly, the negative amyloid status (the standard of truth for this cohort) was presumed rather than confirmed by histopathology. These PET images were read as positive or negative for amyloid. As stated above, this binary reading scale is the sponsor's proposed reading method for Amyvid PET images in routine clinical use.

   For the read sessions of PET images of the young, cognitively normal subjects, additional PET images from 40 autopsy cohort subjects with a median rating on PET images suggestive of amyloid positivity were randomized into the reading queue to minimize bias. Of these 40 autopsy cohort PET images, only 14 had histopathology confirmation. An additional concern is that CT images of some subjects were available to the PET image readers. The reason for this concern is that structural information gleaned from CT images could introduce bias into a reader's decision on amyloid presence or absence based on PET images: young, cognitively normal subjects with a mean age of 26 years

would unlikely demonstrate the cortical atrophy that autopsy cohort subjects with a mean age of 80 years may.

4. There was a statistically significant Spearman's correlation (rho = 0.68 – 0.75, $p<0.0001$) between the semi-quantitative visual ratings of amyloid burden on the PET image for each of 6 cortical regions and the percent area occupied by amyloid measured by quantitative IHC.

5. The subjects in the A07 trial did not represent the population of the intended use. The relatively small sample size of the autopsy cohort reflects the challenges associated with conducting a study requiring histopathology of autopsy specimens as the standard of truth.

6.3 Methods

The methods described in this section were used in the A07 trial unless otherwise specified. The objective of the trial is to assess the relationship between measurements of amyloid with Amyvid PET imaging and true levels of amyloid burden assessed by histology at autopsy. For the autopsy cohort, 152 subjects were enrolled from various end-of-life (hospice/hospital/nursing home) and late-life populations. In order to evaluate the specificity of the drug for detecting the absence of amyloid, a separate cohort of 74 young, cognitively normal and neurologically healthy subjects was enrolled for imaging only. For the latter cohort, the absence of amyloid was presumed.

1. Amyvid dose, image acquisition, safety follow-up: Each subject received a single IV injection of 370 MBq (10 mCi) Amyvid, followed by a saline flush. Image acquisition for 10 minutes occurred around 50 minutes postdose. Subjects were followed up for safety evaluation for 48 hours postdose.

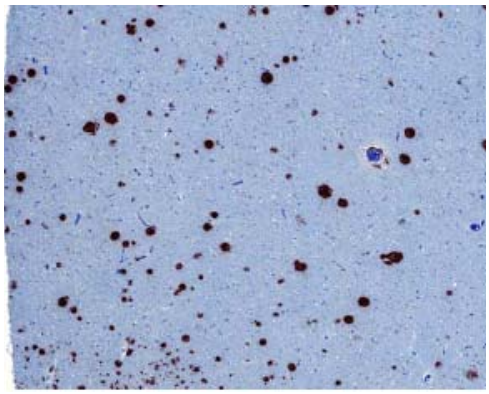
2. PET imaging assessment: For the autopsy cohort, 3 readers blinded to clinical information (readers 1, 2, 3) evaluated images at the imaging core lab (Image Metrix).

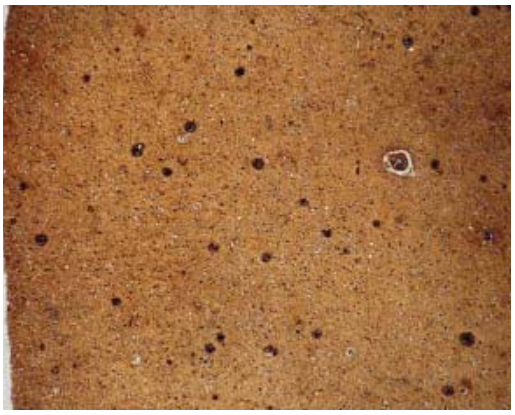
The readers rated each image for overall cortical amyloid burden on a 5-point scale, ranging from 0 (no amyloid) to 4 (high levels of amyloid). Readers provided both global and regional ratings of amyloid deposition. Of the 35 autopsy subjects, 29 were included in the primary endpoint analysis; the 6 "front runners" were used to finalize study methods. In order to calculate performance characteristics, the semi-quantitative 0 - 4 rating was converted to the binary scale using the post-hoc threshold of 1 or lower as negative and 2 or higher as positive.

For the young, cognitively normal cohort, PET images were assessed by three different readers (readers 4, 5, 6) on a binary scale (positive or negative) for amyloid in the gray matter of the whole brain (global) for the primary endpoint. For an additional objective, readers rated the images on a 3-point scale (0 for no amyloid, to 2 for high levels of amyloid) for three regions of the brain (regional).

3. Brain autopsy preparation performed by Sun Health Research Institute (Sun City, AZ): Brain autopsy tissue blocks were dissected into 1 cm^3 sections for each of 7 regions, including 6 regions from the cerebrum (frontal, temporal, parietal lobes, precuneus, anterior cingulate, posterior cingulate) as well as the cerebellum.

4. Immunohistochemistry (IHC) performed by Biospective, Inc. (Montreal, Canada): The brain tissue slides were stained using 4G8 murine monoclonal anti-amyloid antibody as the primary antibody. Pictures of the final slides were digitized and fully automated for quantitating % area occupied by amyloid. A representative picture is on the right:





5. Bielschowsky silver stain performed by Rush University Medical Center (Chicago, IL): Brain tissue slides were stained using the modified Bielschowsky silver staining protocol. A representative picture is on the right. Neuritic plaques were counted by 2 independent trained readers and then reviewed by a neuropathology physician whose plaque count could replace those of the two independent readers. All 3 readers were blinded to the subject's clinical information, PET imaging result and IHC result.

1. Table 3 illustrates a method to convert from the modified Bielschowsky silver stain neuritic plaque counts to the modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque rating scale. At the 11/23/2010 meeting with FDA, the sponsor proposed that the 4-point CERAD neuritic plaque rating scale could be made binary (sparse or none classified as negative) and be used as a truth standard to calculate performance characteristics. Importantly, the A07 Phase 3 trial did use of this method for the truth standard for the primary endpoint.

Table 3. Conversion from Silver Stain Result to CERAD Scale for Neuritic Plaque Counts

Highest Neuritic Plaque Counts	CERAD Neuritic Plaque Scale
0	None
1 – 5	Sparse
6 – 19	Moderate
≥ 20	Frequent

6.4 Demographics

Table 4 summarizes the demographics of the A07 trial:

Table 4: A07 Trial Demographic Characteristics by Cohort*

Characteristic	Autopsy Cohort		Specificity Cohort	
	Subjects Imaged N=152 [a]	Subjects with Autopsy N=29 [b]	Subjects Imaged N=74 [a]	Non-ApoE ε4 Carriers N=47 [b]
Age (years)				
Mean ± SD	78.1 ± 13.35	80.0 ± 13.19	26.6 ± 6.50	26.3 ± 7.17
Median	81.5	85.0	25.5	24.0
Range	38 to 103	55 to 103	18 to 50	18 to 50
Gender				
Male	71 (46.7%)	15 (51.7%)	48 (64.9%)	32 (68.1%)
Female	81 (53.3%)	14 (48.3%)	26 (35.1%)	15 (31.9%)
Race				
Caucasian	134 (88.2%)	26 (89.7%)	57 (77.0%)	36 (76.6%)
Black or African-American	10 (6.6%)	2 (6.9%)	6 (8.1%)	4 (8.5%)
Other	4 (2.6%)	1 (3.4%)	7 (9.5%)	4 (8.5%)
Asian	2 (1.3%)	0	4 (5.4%)	3 (6.4%)
Native American / Alaskan Native	2 (1.3%)	0	0	0
Ethnicity				
Non-Hispanic or Latino	139 (91.4%)	28 (96.6%)	69 (93.2%)	44 (93.6%)
Hispanic or Latino	13 (8.6%)	1 (3.4%)	5 (6.8%)	3 (6.4%)

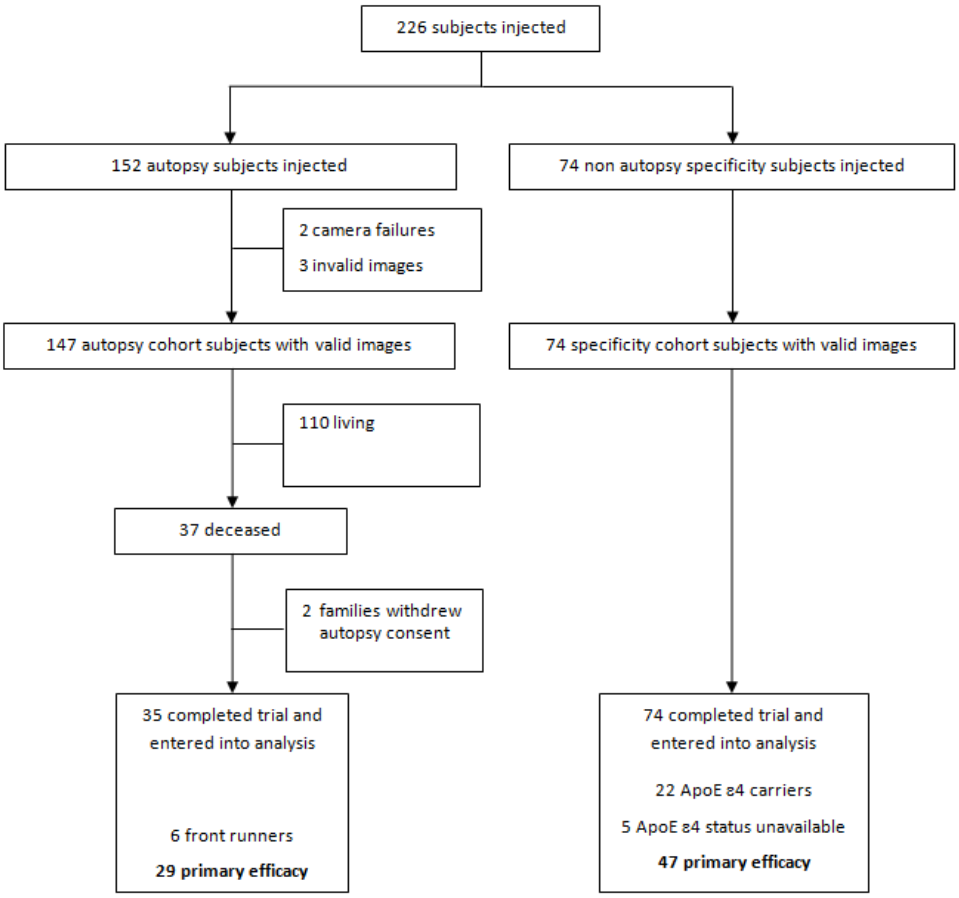
* copied from the NDA submission

Reviewer comments: There is a large difference in mean and median subject age between the autopsy and "specificity" cohorts. The majority of subjects in both cohorts were Caucasians, which reflects the general U.S. population.

6.5 Subject Disposition

The A07 trial enrolled 226 subjects: 152 in the "autopsy" cohort and 74 in the "specificity" cohort. Subject disposition in the A07 trial is summarized in Figure 1:

Figure 1: A07 Trial Subject Disposition*



* copied from the NDA submission

Of the 152 subjects in the "autopsy" cohort, 147 had valid images. At the end of the study, 37 subjects had died in the "autopsy" cohort. Of the 37 subjects in the "autopsy" cohort, 35 completed the trial and had data available for analysis. Of these 35 subjects, 29 were designated as the primary efficacy population and 6 were "front runners" (for finalizing study methods and therefore not included in the primary efficacy analysis).

Of the 74 subjects in the "specificity" cohort, 27 were excluded from the primary efficacy population because they were either ApoE ε 4 allele carriers or their ApoE ε4 genotype was not available. Thus, the 47 control subjects comprised of the primary efficacy population for the specificity analysis.

The 27 protocol deviations in the A07 trial are summarized Table 5:

Table 5: Protocol Deviations in A07 Trial: All Subjects*

	Autopsy Cohort N=152		Specificity Cohort N=74	
Description of Protocol Deviation	**n**	**Subject Number**	**n**	**Subject Number**
Physician not present pre- and post-dose	0	--	11	145-009, 145-010, 145-011, 145-012, 145-013, 145-014, 145-015, 145-016, 145-017, 145-018, 145-020
Wechsler immediate recall score was below study criterion	0	--	3	144-001, 144-009, 271-027
Wechsler immediate and delayed recall scores were below study criteria	0	--	2	321-012, 321-014
MMSE, Wechsler immediate and delayed recall scores were below study criteria	0	--	2	321-007, 321-015
PET scan started significantly more than 80 minutes post-injection	1	054-012	1	062-012
Brain removed more than 24 hours after death	1	059-003	0	--
Subject died more than 1 year after florbetapir-PET imaging	1	134-001	0	--
Subject received a radiation treatment the day before florbetapir-PET imaging	1	062-001	0	--
Subject could not tolerate the 10-minute PET scan	1	060-010	0	--
Subject had hepatitis C	1	064-001	0	--
Subject did not meet inclusion criterion, 18 to 40 years old	0	--	1	140-003
Wechsler delayed recall score was below study criterion	0	--	1	321-013

* copied from the NDA submission

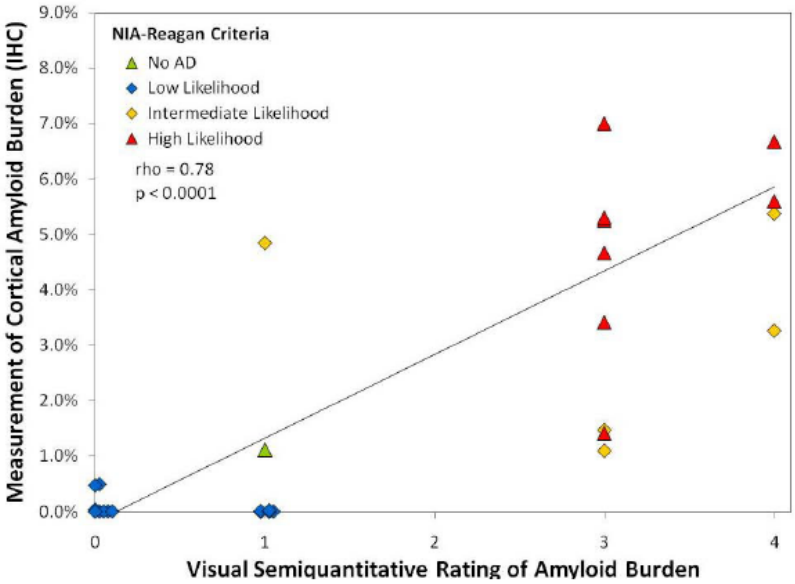
Reviewer comments: There were 27 protocol deviations in the A07 trial (~ 12% of total enrollees). The most common deviation was that the physician was absent before and after tracer administration (11 cases at 1 center). All deviations were considered as minor, and unlikely to have a significant impact on the trial endpoint variables assessed by the reviewer.

6.6 Analysis of Primary Endpoint(s)

6.6.1. "Autopsy" cohort of A07 study

The primary endpoint is a significant correlation between the semi-quantitative visual rating of amyloid burden on the PET scan and the cortical amyloid burden at autopsy as assessed by quantitative IHC. Spearman's Correlation was used to assess the correlation. Figure 2 is the sponsor's correlation result:

Figure 2: Correlation between Semi-quantitative Visual Rating of Cortical Amyloid Burden with Immunohistochemistry (IHC)*



* copied from the NDA submission

Reviewer comments: Although the Spearman's correlation (rho) is statistically significant, the wide vertical distribution of data points for median PET ratings of 1, 3 and 4 suggests that a given PET rating will not likely predict the exact percent cortical amyloid burden. In fact, there were 11 subjects with an immunohistochemistry score of less than 0.05%. For a median PET rating of 3, the IHC % area occupied by amyloid can range from ~1% to ~7%. In the correlation figure above, the Y-axis (IHC result) ranges from 0 to 9%. However, in 2 of the 29 subjects (primary efficacy population), the amyloid burden by IHC was actually over 9% (subject 522-008 with IHC 9.114% and median PET rating of 3, and subject 137-005 with IHC 9.442% and median PET rating of 4, see Table 6 on page 28). It is noted that the median visual read results

segregate predominantly into a 0 to 1 group or a 3 to 4 group with no subjects scored as a 2. This pattern suggests that the subject population was relatively polarized in terms of amyloid deposition with very few or no subjects between the extremes of no amyloid or high amount of amyloid.

Importantly, each data point in Figure 2 represents the median rating from 3 readers, which might obscure inter-reader variability. Analysis of ratings by each of the PET readers (readers 1, 2, 3) confirmed the high variability.

Table 6 summarizes the information on IHC as well as individual reader ratings and median ratings for all 35 subjects who underwent autopsy. Importantly, in 10 of 35 subjects (29%), there is at least 1 reader whose rating of global amyloid burden on PET images differed from that of the other 2 readers by at least 2 ratings on the 5-point scale (0 - 4).

The sponsor's submission defined post-hoc thresholds for converting the various scales to a binary scale as follows: (1) for the semi-quantitative 0 - 4 scale, 0, 1 was considered negative and 2, 3, or 4 as positive, (2) for quantitative IHC, < 1% was considered negative and ≥ 1% as positive, (3) for the number of neuritic plaques on silver staining, ≤5 plaques was considered negative, and > 5 plaques as positive.

Table 6: Inter-reader Variability Analysis of "Autopsy" Cohort

	Subject ID	IHC %	Pos/Neg by IHC*	Reader			
				1	2	3	Median
1	054-002	0.001	Neg	1	1	1	1
2	060-014	0.001	Neg	1	0	3	1
3	145-019	0.001	Neg	1	0	2	1
4	217-006	0.005	Neg	1	0	0	0
5	054-010	0.007	Neg	1	0	0	0
6	057-007	0.007	Neg	1	1	3	1
7	066-021	0.009	Neg	0	0	0	0
8	059-003	0.011	Neg	1	0	0	0
9	217-001	0.011	Neg	1	0	0	0
10	061-010	0.016	Neg	1	0	1	1
11	152-001	0.029	Neg	1	0	1	1
12	062-001	0.042	Neg	1	0	0	0
13	054-003	0.150	Neg	0	0	0	0
14	064-001	0.474	Neg	0	0	0	0
15	061-001	0.492	Neg	0	0	0	0
16	522-001	1.105	Pos	4	3	3	3
17	064-005	1.114	Pos	1	1	0	1
18	062-004	1.418	Pos	4	1	3	3
19	217-003	1.477	Pos	3	1	3	3
20	132-001	3.272	Pos	4	3	4	4
21	134-001	3.421	Pos	4	2	3	3
22	057-002	3.628	Pos	4	1	1	1
23	134-006	4.675	Pos	4	3	3	3
24	522-003	4.852	Pos	1	1	1	1
25	053-001	5.266	Pos	3	1	3	3
26	145-007	5.314	Pos	4	3	3	3
27	134-004	5.385	Pos	4	4	3	4
28	060-004	5.391	Pos	4	1	2	2
29	066-001	5.608	Pos	4	3	4	4
30	217-005	6.686	Pos	4	3	4	4
31	522-005	7.008	Pos	3	1	3	3
32	145-001	7.923	Pos	4	1	4	4
33	134-002	8.621	Pos	4	2	4	4
34	522-008	9.114	Pos	4	3	3	3
35	137-005	9.442	Pos	4	3	4	4

* Post-hoc threshold for IHC: >1% is positive and < 1% is negative for amyloid burden

: Incorrect median rating according to the IHC threshold.

: Rating higher or lower by at least 2 ratings compared to other two readers

: Rating higher or lower by 3 ratings compared to other two readers

Table 7 summarizes performance characteristics as determined by the sponsor:

Table 7: Analysis for Median Visual Rating with Post-hoc NIA-Reagan Threshold*

		Reference Standard: NIA-Reagan		
Florbetapir-PET Image Outcome:		Positive (Intermediate, High) (N=19)	Negative (No AD, Low) (N=16)	
Semi-quantitative Visual Blinded Read	Positive (2,3,4)	18	0	PPV = 100%
	Negative (0,1)	1	16	NPV = 94%
		Sensitivity = 95%	Specificity = 100%	Accuracy = 97%

* copied from the NDA submission

Reviewer comments: NIA-Reagan, the reference standard, is a determination of Alzheimer's disease probability. This determination incorporates not only amyloid burden but also neurofibrillary tangle burden. The amyloid burden used to determine the NIA-Reagan Alzheimer's Disease probability is derived from counting neuritic plaques (silver staining).

The reviewer determined performance characteristics (Table 8) using the 1% IHC threshold as the SOT rather than the NIA-Reagan scale for AD probability since Amyvid is intended to detect amyloid rather than diagnose AD. In addition, the quantitation of amyloid burden by IHC was fully automated and may therefore be less subject to bias compared to silver staining for which plaques are counted by the neuropathologist.

Table 8 demonstrates the following differences: the number of subjects positive by the truth or reference standard increased from 19 to 20, sensitivity decreased from 95% to 85%, and NPV decreased from 94% to 83%. The sensitivity and specificity for each reader and the median read are summarized in Table 9. Reader 2 demonstrates a lower sensitivity (55%) compared to the other readers, which is not surprising given the high inter-reader variability. Accuracy by the individual readers appears as follows: reader 1 > 3 > 2. Based on Table 6 and Table 9, reader 2 appears to have "undercalled", and reader 3 may have "overcalled" some PET images when IHC is the truth standard.

Table 8: Analysis for Median Visual Rating with Post-hoc IHC Threshold

		Neuropathology (IHC)		
		Positive (IHC ≥ 1%), n= 20	Negative (IHC <1%), n=15	
Visual Semi-quantitative Rating	Positive (2, 3, 4)	17	0	PPV = 100%
	Negative (0, 1)	3	15	NPV = 83%
		Sensitivity = 85%	Specificity = 100%	Accuracy = 92%

Table 9: Analysis for Agreement of Median and Individual Visual Rating

	Sensitivity (%)	Specificity (%)
Reader 1	90	100
Reader 2	55	100
Reader 3	85	80
Median	85	100

Summary of the "autopsy" cohort results: Although the primary endpoint of correlation between median PET read on a semi-quantitative 5-point scale (0 - 4) and amyloid burden by IHC was met, several issues--including (a) high inter-reader variability, (b) small sample size of 29, (c) undetermined clinical meaning of post-hoc thresholds, (d) wide range of true amyloid burden for some PET ratings, and (e) absence of the population of intended use in the enrolled subjects--cast doubt on the validity, reproducibility, and clinical utility of Amyvid.

6.6.2. Young, Cognitively Normal Cohort of A07 study

The primary endpoint for this cohort is that the specificity of PET imaging would be ≥ 90% in young, cognitively normal subjects. This endpoint was met (Table 10).

Three readers (readers 4, 5, 6) blind to clinical information rated Amyvid PET images of the 47 young, cognitively normal, ApoE ε4 negative subjects on a binary scale (+ or – for amyloid). The majority PET read was used to determine performance characteristics. Of note, the negative amyloid status of these subjects was presumed rather than confirmed by histopathology. To minimize bias, the sponsor added PET images from the first 40 subjects in the autopsy cohort

whose PET images had a median read of 2, 3, or 4 (suggesting amyloid positivity). Eighty percent of these 40 subjects had a median PET rating of 3 or 4.

Table 10: Sensitivity and Specificity of Visual Assessment in the Young, Cognitively Normal Subjects*

		Reference Standard: Presumed Amyloid Status		
Florbetapir-PET Image Outcome:		Positive (Autopsy Cohort[a]) (N=40)	Negative (Young, Healthy Controls[b]) (N=47)	
Qualitative Visual Blinded Read	Positive (Aβ+)	38	0	PPV = 100%
	Negative (Aβ-)	2	47	NPV = 96%
		Sensitivity = 95%	Specificity = 100%	Accuracy = 98%

* copied from the NDA submission

Reviewer comments: A significant limitation of this endpoint is that the young, cognitively normal subjects do not truly represent a "specificity" cohort since they are not in the population of intended use. The true specificity cohort would comprise of subjects presenting with memory impairment or cognitive decline who are confirmed to be negative for amyloid. Furthermore, although there is high specificity in the cohort, the absence of amyloid in these young subjects is presumed rather than confirmed by pathology. The reviewer will focus on the "specificity" cohort data analysis since the PET image readers for this cohort applied the binary interpretation method, and this is the sponsor's proposed method for routine clinical use if Amyvid is approved. A total of 74 were enrolled in the cohort, but only 47 subjects were confirmed as negative carriers of ApoE ε4 (genetic risk factor for AD). Thus, data from only these 47 subjects were used in the primary endpoint analysis for this cohort. Specificity results for each individual reader are summarized in Table 11.

Table 11: By-reader Specificity for the 47 Young, Cognitively Normal Subjects

	Read Negative / Presumed Negative	%
Reader 4	47 / 47	100
Reader 5	46 / 47	98
Reader 6	47 / 47	100
Majority	47 / 47	100
All Reads	140 / 141	99

The sponsor added PET images from 40 subjects in the "autopsy" cohort into the "specificity" cohort image pool to minimize bias. The images from these 40 subjects had a median PET read by Readers 1, 2, and 3 suggestive of amyloid presence (median rating of 2, 3, or 4 on a 5-point scale). Of these 40 PET images, 38 (95%) were also read as positive for amyloid by the majority of Readers 4, 5, and 6 (Table 12, Table 13). Only 14 of these 40 subjects underwent autopsy and had pathology results. PET images of all 14 subjects were interpreted as positive by majority read; only 2 of these PET images were read as negative, each by a single reader so the majority read was not affected (Table 12, Table 14).

Ideally, PET images from all 35 subjects in the "autopsy" cohort would have been randomized into the image pool of the "specificity" cohort for assessment of performance characteristics using the binary scale for PET images and pathology as the standard of truth. An additional concern is that structural information on CT images (when available) could have biased readers regarding amyloid presence or absence: the young, cognitively normal subjects (mean age of 26) would likely show less cortical atrophy than the "autopsy" cohort subjects (mean age of 80).

Table 12: Summary of 40 "Autopsy" Subjects (PET Images Randomized in with Those from Young, Cognitively Normal Subjects)*

	Subject	Neuritic Plaque (CERAD)*	Reader			
			4	5	6	Majority
1	522-001	More than sparse	Pos	Pos	Pos	Pos
2	062-004		Pos	Pos	Pos	Pos
3	217-003		Pos	Pos	Neg	Pos
4	134-001		Pos	Pos	Pos	Pos
5	134-006		Pos	Neg	Pos	Pos
6	053-001		Pos	Pos	Pos	Pos
7	145-007		Pos	Pos	Pos	Pos
8	060-004		Pos	Pos	Pos	Pos
9	066-001		Pos	Pos	Pos	Pos
10	217-005		Pos	Pos	Pos	Pos
11	145-001		Pos	Pos	Pos	Pos
12	134-002		Pos	Pos	Pos	Pos
13	522-008		Pos	Pos	Pos	Pos
14	137-005		Pos	Pos	Pos	Pos
15	057-001	NA	Neg	Neg	Neg	Neg
16	057-005		Pos	Pos	Pos	Pos
17	059-001		Pos	Pos	Pos	Pos
18	059-005		Pos	Pos	Pos	Pos
19	059-006		Pos	Pos	Pos	Pos
20	059-012		Pos	Neg	Pos	Pos
21	060-001		Pos	Pos	Pos	Pos
22	060-003		Pos	Pos	Pos	Pos
23	060-005		Pos	Neg	Pos	Pos
24	060-006		Pos	Pos	Pos	Pos
25	062-002		Pos	Pos	Pos	Pos
26	062-003		Pos	Pos	Pos	Pos
27	062-005		Pos	Pos	Pos	Pos
28	064-002		Pos	Pos	Pos	Pos
29	129-001		Pos	Pos	Pos	Pos
30	129-004		Neg	Neg	Neg	Neg
31	134-005		Pos	Pos	Pos	Pos
32	137-001		Pos	Pos	Pos	Pos
33	145-002		Pos	Pos	Pos	Pos
34	145-003		Pos	Pos	Pos	Pos
35	145-004		Pos	Pos	Pos	Pos
36	145-005		Pos	Pos	Pos	Pos
37	145-006		Pos	Neg	Pos	Pos
38	522-002		Pos	Pos	Pos	Pos
39	522-004		Pos	Pos	Pos	Pos
40	522-007		Pos	Pos	Pos	Pos

* only 14 of the 40 subjects underwent autopsy, and all were "more than sparse" for neuritic plaques (≥ 6 neuritic plaques in the microscopic field)

Table 13 summarizes the by-reader "sensitivity" for the 40 subjects from the "autopsy" cohort whose images were randomized into the image pool from the young, cognitively normal subjects. "Sensitivity" is in quotes here because the reference standard was the median read by a different set of readers rather than pathology. Only 14 of these 40 subjects had histopathology results as the standard of truth (Table 14).

Table 13: By-reader "Sensitivity" for the Presumed Positive Group (PET Images Randomized in with Those from Young, Cognitively Normal Subjects), n=40*

	Read Positive per Positive by "Autopsy" Cohort Readers*	%
Reader 4	38 / 40	95
Reader 5	34 / 40	85
Reader 6	37 / 40	93
Majority	38 / 40	95
All Reads	109 / 120	91

* Fourteen of 40 subjects had histopathology result, all 14 with "more than sparse" neuritic plaques

Table 14: By-reader Sensitivity for the Pathology Confirmed Positive Group (PET Images Randomized in with those from Young, Cognitively Normal Subjects), n=14*

	Read Positive per Silver Staining "More Than Sparse" for Neuritic Plaques	%
Reader 4	14 / 14	100
Reader 5	13 / 14	93
Reader 6	13 / 14	93
Majority	14 / 14	100
All Reads	40 / 42	95

* All 14 had histopathology result of "more than sparse" neuritic plaques

Readers 4, 5, and 6 read PET images for 114 subjects: 74 subjects were young and cognitively normal, the other subjects were the first 40 from the "autopsy" cohort with amyloid-positive images according to Readers 1, 2, and 3 (median read $\geq$ 2). The inter-reader agreement among the 3 readers for these 114 images is over 90% (Table 15):

Table 15: Inter-reader Agreement for Visual Qualitative Binary Rating of PET Images from 74 Young, Cognitively Normal and 40 "Autopsy" Cohort Subjects*

	n	Observed Agreement (%)	Kappa Statistic	95% CI
Reader 4 vs. Reader 5	114	94	0.86	0.76 - 0.96
Reader 4 vs. Reader 6	114	99	0.98	0.94 - 1.00
Reader 5 vs. Reader 6	114	93	0.84	0.73 - 0.95

* copied from the NDA submission

Summary of the "specificity" cohort results: Although the primary endpoint of >90% specificity in the 47 young, cognitively normal subjects was met, the amyloid negative status (SOT) was presumed rather than confirmed by pathology. Although the majority read was positive for all "autopsy" cohort subjects randomized into the image pool, there were only 14 subjects whose amyloid positive status was confirmed by the pathology. Ideally, PET images of all 35 subjects who underwent autopsy would have been randomized into the image pool of the "specificity" cohort so that performance characteristics of the sponsor's proposed reading method for routine clinical use of Amyvid PET images could be assessed relative to amyloid status by pathology.

6.6.3 A05 study

A05 was a Phase 2 study that examin**ed** Amyvid images among subjects with a relatively broad range of cognition. This study used both a semi-quantitative read method as well as the binary method that the company has proposed for ultimate clinical use. Hence, this study's result**s** are particularly useful for estimating the reader to reader reproducibility of the binary read method among a population with a wide range of cognitive ability. This study enrolled subjects with different cognitive abilities: 79 healthy controls with normal cognitive function over 50 years of age, 60 patients with a clinical diagnosis of MCI, and 45 patients with an Alzheimer's disease diagnosis (Table 16).

Importantly, the Phase 3 A07 binary read population constitutes of what appears to represent the extremes of amyloid burden, since the population consisted of two very distinct groups - young healthy subjects in contrast to end of life subjects who had high amyloid burdens on a previous read of their Amyvid scans. Hence, the image reads of Phase 3 subjects are not representative of subjects who may have intermediate levels of amyloid in the brain. It is this intermediate subject

population (represented in the Phase 2 Study A05) in which Amyvid, if approved, might ultimately find its greatest use. In addition, the ability to detect gross atrophy on PET images conceivably could have biased the image interpretations, particularly given the difference between healthy young subjects and end of life subjects. The potential importance of Amyvid's role in the assessment of subjects with intermediate levels of brain amyloid is somewhat illustrated by the binary read results from Study A05.

Table 16. Result Summary of A05 Study*

Amyloid	HV n = 78	MCI n = 60	AD n = 45
Positive	11 (14%)	23 (38%)	34 (76%)
Negative	67 (86%)	37 (62%)	11 (24%)

* HC: healthy control with normal cognitive function and over 50 yrs old

Reviewer comments: Based on Table 16, the images positive for amyloid were obtained in approximately 14% of the healthy controls, 38% of the patients with mild cognitive impairment and 76% of the patients with Alzheimer's disease. Since this study lacked a truth standard, it is not possible to determine the reliability of these imaging results: we do not know whether the 14% of healthy controls truly have brain amyloid deposition. Nevertheless, the results emphasize the importance of having a reliable assessment method, particularly for patients who may have intermediate levels of brain amyloid.

Although there appears to be relatively good reproducibility of image reads within the 114 subjects of specificity cohort and 40 subjects from autopsy cohort of A07, it appears that the inter-reader agreement of the PET imaging interpretation from A05 is not as high as the result from the A07. Please see the detailed analysis in the statistical review of the NDA.

6.7 Analysis of Secondary Endpoints(s)

The secondary endpoint of the A07 trial is regional correlation between visual rating (0-4 scale) of the PET images and cerebral amyloid burden by immunohistochemistry (IHC) (Table 17). These results were verified by the reviewer.

Table 17: Regional Correlation Between Semi-quantitative Visual Ratings (0-4) of Cerebral Amyloid Burden with Immunohistochemistry (IHC), n=35*

	Avid Analysis		Reviewer Analysis	
	Spearman's rho	95% CI	Spearman's rho	95% CI
Frontal	0.69	0.44, 0.84	0.71	0.48, 0.84
Temporal	0.68	0.42, 0.84	0.68	0.44, 0.82
Precuneus	0.75	0.53, 0.88	0.76	0.56, 0.87
Parietal	0.77	0.56, 0.88	0.72	0.50, 0.84
Ant Cingulate	0.74	0.51, 0.87	0.75	0.54, 0.84
Post Cingulate	0.70	0.44, 0.85	0.68	0.43, 0.82

* 95% CI: 95% confidence interval

6.8 Other Endpoints

1. Based on the exploratory endpoint analysis, the sponsor claimed that
   - "The correlation between the quantitative SUVR analysis of the florbetapir-PET images and the cortical amyloid burden assessed by quantitative IHC was 0.76 ($p < 0.0001$, 95% CI: 0.56 – 0.87)" and

   - SUVR analysis (using the post-hoc 1.10 positive cutoff) showed 100% sensitivity and specificity with autopsy results.

Reviewer comment: SUVR is a multifactorial equation generated from SUV (standard uptake value). SUV indicates the radioactive signal of the PET tracer in the specific area. SUV is a quantitative parameter in the PET functional imaging assessment and widely used in the FDG [Fludeoxyglucose (F-18)] PET imaging interpretation. But SUV can be affected by many factors, including image noise, low image resolution, and user biased region of interest (ROI) selection [14]. SUVR can be affected by more factors than SUV. According to the protocol, there were multiple steps for the SUVR calculation "*the SUVR in the submission is the ratio of cortical to cerebellar signal, which were calculated for the following 6 target cortical brain regions: frontal, temporal, precuneus, parietal cortex, anterior cingulate, and posterior cingulate using whole cerebellum as the reference region. The main SUVR efficacy endpoint for quantitative evaluation of each subject was the mean of the SUVRs for the 6 cortical target regions.*" Obviously, each step described above can influence the SUVR value. The reviewer

considers a ratio as a fraction, here the cerebral SUV as numerator and the cerebellar SUV as denominator. Application of the ratio here is based on the assumption that (a) the cerebellar SUV (denominator) is relatively stable and not closely correlated with cerebral SUV (numerator), and (b) there is good correlation between the cerebral SUV and SUVR--that is, SUVR increases with the increase of cerebral SUV and vice versa. However, detailed data analysis shows that these assumptions are violated: there is wide variability in cerebellar SUV ranging from 0.038 to 2.294 (0.774 ± 0.484 [mean ± SD]), see 8. The data demonstrate that there is good correlation between cortical SUV and cerebellar SUV with a Pearson's correlation of 0.92 ($p < 0.0001$) and an unimpressive correlation between the cortical SUV and SUVR with Pearson's correlation of only 0.5 (though still statistically significant with $p = 0.003$). Pearson's analysis rather than Spearman analysis is used here since both SUV and SUVR are continuous variables. According to the sponsor, the total sample size for the analysis is 33, and two SUV data sets are missing. The SUVR cutoff of 1.1 is a post-hoc threshold which might be misleading. Analysis of the available data demonstrates that the range of SUVR is quite narrow [from 0.81 (minimal) to 1.91 (maximal) (n = 35)] whereas the range of IHC is quite broad, [from 0.001 to 9.44 (Table 18)], suggesting that SUVR values did not reflect the histopathology results quantitatively.

Table 18: Statistics of Pathology (IHC and Silver Stain) and Quantitative Imaging Parameters (SUV and SUVR) in "Autopsy" Cohort

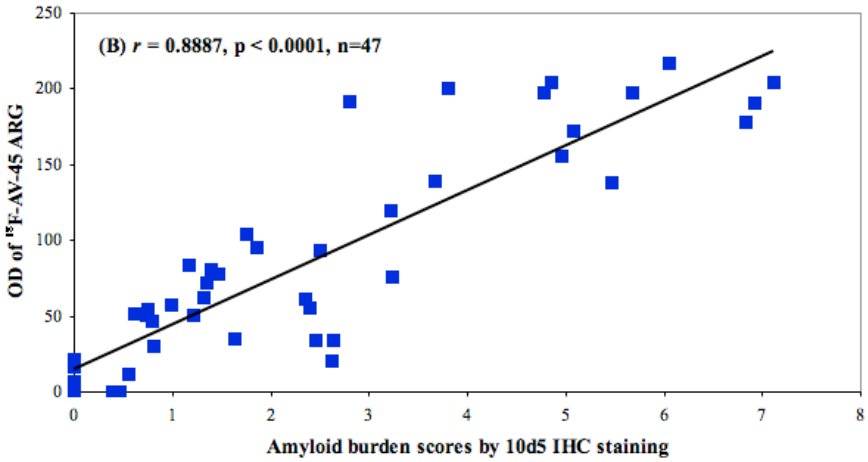
Variable	n	Mean	SD	Median	Minimum	Maximum
Cerebral IHC	35	2.914	3.161	1.418	0.001	9.442
SUVR	35	1.207	0.284	1.196	0.807	1.911
Cerebral SUV	33	0.964	0.699	0.788	0.037	3.735
Cerebellar SUV	33	0.774	0.484	0.736	0.038	2.294

Overall, there is no solid evidence available to demonstrate that SUVR is an accurate and reliable quantitative parameter for PET imaging assessment for brain amyloid deposition.

2. The strong *in vitro* correlation using radiolabeled Amyvid does not translate into high *in vivo* correlation using Amyvid. The sponsor claimed that the preclinical studies showed that the drug selectively binds to and labels amyloid in human brain tissue and that binding intensity

of the drug is quantitatively correlated with the density of amyloid quantified by IHC (Figure 3).

Figure 3: Correlation between Amyvid Autoradiography Signal Intensity (Optical Density, OD) with Amyloid Aggregate Deposition Measured by Immunohistochemistry (IHC)*



* copied from the NDA submission

Reviewer comments: Although the *in vitro* correlation may be impressive, the *in vivo* correlation between cortical global or regional PET imaging signal (SUV) and amyloid burden measured by IHC (Table 19) is not as high.

Table 19: Correlation between Global and Regional Signal (SUV) and Amyloid Burden (IHC), n=33

	Pearson's r
Cerebral Global	0.50
Frontal	0.49
Temporal	0.45
Precuneus	0.48
Parietal	0.45
Ant Cingulate	0.51
Post Cingulate	0.49

3. Not all PET images in the A07 trial were acquired with CT. Nowadays; PET/CT fusion is almost routine for functional imaging acquisition and interpretation. CT imaging allows functional imaging obtained by PET, which depicts the spatial distribution of metabolic or biochemical activity in the body, to be more precisely aligned or correlated with anatomic imaging. According to the submission, 40 of the 221 PET images in the A07 trial were

acquired without CT. This raises the possibility that inconsistent CT acquisition may have introduced variability into the results.

6.9 Subpopulations

Because Amyvid is intravenously administered, fully bio-available, and very rapidly cleared from plasma, pharmacokinetic studies in special populations were not performed. However, population analysis of PET scan data revealed no difference in drug binding and blood clearance kinetics in probable AD patients or cognitively healthy controls. No significant differences were seen among individuals of different gender, race and age.

6.10 Analysis of Clinical Information Relevant to Dosing Recommendations

Study A03 evaluated the range of effective doses for Amyvid. Twenty subjects (9 AD, 11 healthy controls) were enrolled in the study. Nine subjects and 11 subjects were assigned to the 111 MBq (3 mCi) and 370 MBq (10 mCi) dose groups, respectively. Images were evaluated qualitatively to determine acceptable image quality between 3 and 10 mCi dose levels. A blinded reader rated the quality of each image on a 5-point scale (where a score of 5 = excellent and 1 = poor). Visual assessments of image quality were better for the 370 MBq dose than the 111 MBq dose group although there was no significant difference. Based on the improvement in the visual image quality ratings, a dose of 370 MBq was recommended as the reference dose for clinical application and for all subsequent clinical trials.

6.11 Discussion of Persistence of Efficacy and/or Tolerance Effects

A03 study also evaluated the optimal time window (time from the tracer injection to proposed imaging in clinical use) of Amyvid. The result showed very stable brain radioactive signal between 30 and 90 minutes after injection and imaging acquisition 30 - 50 minutes post drug injection was decided accordingly.

6.12 Additional Efficacy Issues/Analyses

A04 study evaluated the test-retest reproducibility of Amyvid PET imaging. Twenty subjects

(10 clinically diagnosed AD and 10 healthy controls) were imaged twice on 2 separate days with 1 month. The images were read by a single reader with binary qualitative (amyloid positive or negative) reading and the result is summarized in Table 20:

Table 20: Agreement for Binary Assessment between Test and Retest Images

	n	Agreement (%)	Kappa (95% CI)
Probable AD	10	90	0.74 (0.26, 1.00)
Healthy Control	10	100	1.00 (1.00, 1.00)

7 Review of Safety

Safety Summary

Safety data for Amyvid from all 7 clinical studies (n = 496 subjects) reveal no important safety signals for Amyvid administration. There have been no deaths or serious adverse events (SAE) attributable to the drug as determined by the study investigators. The safety data from clinical laboratory evaluations, vital sign monitoring, and ECG assessments have produced no important concerns regarding Amyvid use.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from the 496 subjects who received at least one dose of Amyvid in clinical trials is summarized in Table 21:

Table 21: The Studies in the Integrated Safety Analysis

Phase	Study ID	Subjects # (n)	Dosing (IV administration)
1	A01	32	10 mCi, single
	A02	9	10 mCi, single
	A03	20	3 mCi and 10 mCi single
	A04	25	10 mCi 2 doses within 4 weeks
2	A05	184	10 mCi, single
3	A07	226	10 mCi, single
		Total 496	

7.1.2 Categorization of Adverse Events

Treatment-emergent adverse event (TEAE) is an undesirable experience, sign, or symptom that started, or worsened, in intensity or frequency at the time of or 48 hours after the administration of Amyvid.

An SAE can result in any of the following outcomes including death, life-threatening, inpatient hospitalization, persistent or significant disability, congenital anomaly or birth defect, or other important medical events.

The assessment of the relationship of an AE to the administration of the drug (remote, possible, and probable) was made using all available information. The intensity/severity of an AE is classified as mild, moderate and severe.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Amyvid safety data were pooled across the 7 clinical studies with a total of 496 subjects summarized in Table 21 (section 7.1.1 above).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All 496 patients exposed were adults > 18 years of age who received at least one administration of Amyvid ranging from 3 mCi to 10 mCi (the proposed dosage). Twenty five subjects in A04 test-retest trial received two doses of the drug within one month, summarized in the section 6.1.10 above. There is no specific sample size required for radiopharmaceutical safety assessment according to FDA guidelines. The data from 496 subjects appear adequate.

7.2.2 Explorations for Dose Response

The phase 1 A03 study compared the 3 mCi and 10 mCi doses of Amyvid administered with regards to dose escalation estimates. The final, proposed dose of 10 mCi was determined based upon adequate imaging results and acceptable radiation dosimetry estimates obtained in the phase 1 studies.

7.2.3 Special Animal and/or In Vitro Testing

The pre-clinical safety pharmacology studies did not reveal risk of adverse effects of the drug on the CNS or the cardiovascular system, with the NOAEL at least 100-fold higher than the maximum intended dose from a single dose of the drug to humans.

7.2.4 Routine Clinical Testing

The routine clinical testing of study subjects was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

[Please see Clinical Pharmacology section (4.4.2) for further details]

There have been no human studies to investigate Amyvid drug interactions. Drug interactions with Amyvid are considered unlikely based on the nature and action mechanism of the drug.

Amyvid use in patients with impaired excretory or metabolic function has not been evaluated because of its single dose, microgram dosing regimen. The effects of age and gender differences on the drug pharmacokinetics have not been evaluated.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Amyvid is a new molecular entity and pharmacological effects from the drug are not observed in humans following the intravenous administration of the proposed dose of ≤ 50 μg. The non-radioactive ingredient of the drug is an analog of PiB, which is a fluorescent analog of thioflavin T. There are multiple PiB and PiB analog PET radio-tracers with radioisotope of F-18, C-11, and I-123 [for Single photon emission computed tomography (SPECT)] in clinical trials under IND. The first human study with PiB-C-11 was in 2004 [9]. There have been thousands of human subjects who have been administered the PiB PET tracer, and safety data of the drug appears benign.

7.3 Major Safety Results

7.3.1 Deaths

There were a total of two death reports with administration of Amyvid. The cause of death of both cases was considered un-related to Amyvid. The first case was a 78-year-old hospice dwelling male with Parkinson's disease and dementia in A07 who experienced a severe AE and died from respiratory failure around 29 hours post-dosing, during the 48-hour safety monitoring period. The relationship of the death to the drug was considered remote (unlikely) by the investigator at the site. The second death case was outside of the Avid-sponsored clinical studies. An 83-year-old male AD patient with multiple medical issues was in a therapy trial in which Amyvid was used as an imaging biomarker for therapeutic effect. The subject experienced a fatal hemorrhagic stroke one day after dosing and died two days later. The causal relationship of death to the drug was deemed unlikely by the site investigator.

7.3.2 Nonfatal Serious Adverse Events

There were two non-fatal SAEs and both were considered unrelated to Amyvid administration. One was an upper limb fracture 4 days post dosing. Another one outside of the Avid trial suffered an acute stroke 2 days after dosing.

7.3.3 Dropouts and/or Discontinuations

No subject withdrew from the Amyvid studies due to a TEAE.

7.3.4 Significant Adverse Events

For the safety population, the overall rate of AEs was low, with 47 of 496 (9.5%) subjects experiencing a total of 63 TEAEs (Table 22). The majority of these AEs were assessed to be mild and not related to the study drug. The most frequently reported adverse events (in descending order of frequency) were headache (9 of 496 [1.8%] subjects), musculoskeletal pain (4 of 496 [0.8%] subjects), fatigue (3 of 496 [0.6%] subjects), and nausea (3 of 496 [0.6%] subjects). Cognitively impaired subjects showed no evidence for having an increased rate of AEs.

Table 22: TEAE in Descending Order of Frequency – Safety Population*

MedDRA Preferred Term (PT)	No. (%)[a]		
	Cognitively Impaired (N = 247)	Cognitively Normal (N = 249)	Overall (N = 496)
Number of Subjects With at Least One Adverse Event	**18 (7.3)**	**29 (11.6)**	**47 (9.5)**
Headache	5 (2.0)	3 (1.2)	8 (1.6)
Musculoskeletal pain	1 (0.4)	3 (1.2)	4 (0.8)
Fatigue	1 (0.4)	2 (0.8)	3 (0.6)
Nausea	0	3 (1.2)	3 (0.6)
Anxiety	0	2 (0.8)	2 (0.4)
Back pain	1 (0.4)	1 (0.4)	2 (0.4)
Claustrophobia	0	2 (0.8)	2 (0.4)
Hypertension	1 (0.4)	1 (0.4)	2 (0.4)
Insomnia	1 (0.4)	1 (0.4)	2 (0.4)
Neck pain	2 (0.8)	0	2 (0.4)
Abdominal distension	1 (0.4)	0	1 (0.2)
Blood pressure increased	1 (0.4)	0	1 (0.2)
Chest pain	0	1 (0.4)	1 (0.2)
Chills	1 (0.4)	0	1 (0.2)
Constipation	1 (0.4)	0	1 (0.2)
Diarrhoea	0	1 (0.4)	1 (0.2)
Dizziness	0	1 (0.4)	1 (0.2)
Dysgeusia[b]	0	1 (0.4)	1 (0.2)
Feeling cold	0	1 (0.4)	1 (0.2)
Flatulence	0	1 (0.4)	1 (0.2)
Flushing	0	1 (0.4)	1 (0.2)
Haematuria	0	1 (0.4)	1 (0.2)
Infusion site extravasation	1 (0.4)	0	1 (0.2)
Infusion site rash	0	1 (0.4)	1 (0.2)
Injection site haemorrhage	0	1 (0.4)	1 (0.2)
Injection site irritation	0	1 (0.4)	1 (0.2)
Musculoskeletal stiffness	1 (0.4)	0	1 (0.2)
Oedema peripheral	1 (0.4)	0	1 (0.2)
Pain	0	1 (0.4)	1 (0.2)
Palpitations	0	1 (0.4)	1 (0.2)
Parosmia	0	1 (0.4)	1 (0.2)
Pruritus generalized	0	1 (0.4)	1 (0.2)
Respiratory failure	1 (0.4)	0	1 (0.2)
Sinus headache	0	1 (0.4)	1 (0.2)
Supraventricular extrasystoles	1 (0.4)	0	1 (0.2)
Upper limb fracture	1 (0.4)	0	1 (0.2)
Urine color abnormal	1 (0.4)	0	1 (0.2)
Urticaria	0	1 (0.4)	1 (0.2)
Ventricular extrasystoles	1 (0.4)	0	1 (0.2)
Vessel puncture site haematoma	0	1 (0.4)	1 (0.2)
Vomiting	0	1 (0.4)	1 (0.2)
White blood cell count increased	0	1 (0.4)	1 (0.2)

* copied from the NDA submission

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent adverse events (TEAE) are those AEs experienced anytime following administration of Amyvid. In the safety population, 47 of 496 (9.5%) subjects experienced a total of 63 TEAEs with the top five being headache, musculoskeletal pain, fatigue, nausea and anxiety (Table 22 in section of 7.3.4 above).

7.4.2 Laboratory Findings

There were no clinically meaningful predose to postdose changes in the mean values associated with any laboratory value. While some predose to postdose changes reached statistical significance ($P < 0.05$), many moved in a non-detrimental direction (e.g., decrease in liver enzymes). Most of the potentially clinically significant (PCS) laboratory values in individual subjects were also PCS at the predose or screening laboratory values. In addition, only 1 of 496 subjects in the Safety Population had clinical laboratory value that was considered an AE by the principal investigator (increase of white blood cell count (WBC) from 9.9 predose to 11.2 postdose).

7.4.3 Vital Signs

The vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, respiratory rate, and body temperature, were measured at baseline, 0, 75, and > 110 minutes postdose. Statistically significant increases in blood pressure were seen between screening and baseline measurements (i.e., prior to administration of drug) as well between baseline and both t = 0 and t = 75 minutes post dose. The changes in individual subjects occasionally met criteria for potential clinical significance, particularly at the 75-minute postdose measurement (Table 23). However, since this was the time point when the patient was getting off of the table from the PET procedure, changes at this time point could be procedural. In general, the subjects that had changes that met criteria for potential clinical significance had evidence for more general blood pressure variability with significant increases in blood pressure levels prior to study drug administration (i.e. the predose blood pressure was increased as compared to screening). The

changes in blood pressure after drug administration were generally not thought to be clinically significant by the site investigators and all resolved without treatment.

Table 23: SBP and DBP Change from Baseline to Postdose (in Minutes)*

Paramter Postdose Time Point (min)	Statistic	Modified Safety Population, No. (%)			No. (%)
		Cognitively Impaired (N = 145)	Cognitively Normal (N = 199)	Overall (N = 344)	A07 AC Subjects (N = 152)
Systolic blood pressure, mmHg					
0	N	145	115	260	—
	Mean (SD)	2.2 (9.03)	3.1 (10.43)	2.6 (9.67)	—
	95% CI	0.74, 3.70	1.13, 4.98	1.41, 3.77	—
	Median	2.0	2.0	2.0	—
	Min, Max	–27, 34	–24, 58	–27, 58	—
	P value	0.0036	0.0021	< 0.0001	—
75	N	140	185	325	151
	Mean (SD)	4.6 (12.85)	0.8 (11.31)	2.4 (12.13)	3.8 (15.17)
	95% CI	2.43, 6.73	–0.86, 2.42	1.09, 3.74	—
	Median	4.0	0.0	2.0	2.0
	Min, Max	–47, 66	–30, 44	–47, 66	–41, 47
	P value	< 0.0001	0.3521	0.0004	0.0023
> 110	N	24	39	63	—
	Mean (SD)	–2.4 (13.78)	4.7 (13.77)	2.0 (14.09)	—
	95% CI	–8.19, 3.44	0.23, 9.15	–1.55, 5.55	—
	Median	–1.5	7.0	3.0	—
	Min, Max	–28, 26	–30, 46	–30, 46	—
	P value	0.4071	0.0398	0.2642	—
Diastolic blood pressure, mmHg					
0	N	145	115	260	—
	Mean (SD)	1.8 (5.94)	0.6 (5.55)	1.3 (5.79)	—
	95% CI	0.81, 2.76	–0.41, 1.64	0.56, 1.97	—
	Median	2.0	0.0	1.0	—
	Min, Max	–23, 19	–25, 18	–25, 19	—
	P value	0.0004	0.2388	0.0005	—
75	N	140	185	325	151
	Mean (SD)	3.2 (7.25)	1.0 (6.74)	2.0 (7.04)	3.4 (10.44)
	95% CI	2.00, 4.43	0.07, 2.02	1.21, 2.75	—
	Median	3.0	0.0	2.0	2.0
	Min, Max	–21, 26	–28, 21	–28, 26	–26, 40
	P value	< 0.0001	0.0367	< 0.0001	< 0.0001
> 110	N	24	39	63	—
	Mean (SD)	1.7 (9.27)	0.9 (7.69)	1.2 (8.27)	—
	95% CI	–2.21, 5.62	–1.57, 3.42	–0.86, 3.30	—
	Median	0.0	1.0	1.0	—
	Min, Max	–17, 28	–21, 16	–21, 28	—
	P value	0.3761	0.4583	0.2450	—

* copied from the NDA submission

7.4.4 Electrocardiograms (ECGs)

The ECG was tested from baseline to 0, 75, and > 110 minutes postdose (Table 24). In the 344 subjects with pre and post treatment ECG results, there was a statistically significant finding with

a small (3 msec) mean increase in QTcF at the 75 minute post dose time point (shortly after completion of imaging). This change in mean QTcF may be a consequence of the algorithm used to correct for heart rate decrease rather than a true physiologic change, as the algorithm tends to under-correct when heart rate is low and produce spurious high QTc values. This is supported by the observation that the mean QTcB did not change significantly from Baseline at any postdose time point. No individuals had increases in QTcF or QTcB more than 60 msec from baseline, and no absolute QTc values exceeded 500 msec. The results suggest the drug has no significant effect on cardiac electrophysiology.

Table 24: ECG Results: Changes from Baseline to Postdose (in Minutes)*

ECG Measurement Postdose Time Point	Statistic	Modified Safety Population, No. (%)		
		Cognitively Impaired (N = 145)	Cognitively Normal (N = 199)	Overall (N = 344)
QTcF for Fridericia's Correction Formula, msec				
0 min	N	142	112	254
	Mean (SD)	0.2 (8.91)	0.7 (7.56)	0.4 (8.33)
	95% CI	–1.24, 1.72	–0.75, 2.08	–0.60, 1.46
	Median	0.0	0.0	0.0
	Min, Max	–46, 21	–16, 23	–46, 23
	P value	0.7493	0.3528	0.4138
75 min	N	139	110	249
	Mean (SD)	2.7 (10.95)	3.5 (14.76)	3.0 (12.75)
	95% CI	0.83, 4.50	0.70, 6.27	1.44, 4.62
	Median	2.0	4.0	3.0
	Min, Max	–28, 42	–106, 28	–106, 42
	P value	0.0048	0.0148	0.0002
> 110 min	N	25	33	58
	Mean (SD)	–1.1 (9.93)	0.9 (10.21)	0.1 (10.05)
	95% CI	–5.16, 3.03	–2.72, 4.52	–2.59, 2.69
	Median	1.0	0.5	0.6
	Min, Max	–28, 15	–32, 24	–32, 24
	P value	0.5961	0.6166	0.9689

* copied from the NDA submission

Reviewer comments: The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the cardiac electrical cycle. The QT interval generally represents electrical depolarization and repolarization of the left and right ventricles. The standard clinical values QTc (corrected QT), either QTcB calculated with Bazett's correction formula or QTcF with Fridericia's formula. According to the FDA guideline, the normal QTc is defined as equal to or less than ≤ 400 msec (0. 40 sec), abnormal if > 450 msec and the thresholds for trial discontinuation increases in QT/QTc to > 500 msec or of > 60 msec over baseline [15]. The

small increase of an average of 3 msec of QTcF appears to not have a significant impact on cardiac electrophysiology.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

None

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

One phase 1 study (A03) compares the 3 mCi and 10 mCi doses with a small sample size of 20 subjects. Analysis of safety data from the study indicated no significant difference between the subjects receiving the two different doses.

7.5.2 Time Dependency for Adverse Events

According to the submission, the time of onset, duration, action taken, and outcome of AEs were 48 hours post-injection of the drug. See further details in section 7.5.3 below.

7.5.3 Drug-Demographic Interactions

The incidence of AEs with Amyvid was analyzed in the subgroups including gender, race and age. TEAEs for the safety population (n = 496) are analyzed separately for geriatric (≥ 65 years old) (n = 307) and non-geriatric (< 65 years old) (n = 189) subpopulations. There is no consistent difference in the pattern of adverse events between males and females. There is no evidence of any tolerability or special AE concerns that are specific to the geriatric subpopulation. There was no clinically significant interaction of age with lab parameters following drug administration. The only change from baseline in vital signs by age category is increase of blood pressure (see section 7.4.3). ECG with age data showed that the small but statistically significant increase in QTcF that was seen in the whole population at 75-minute postdose was similar in magnitude in both the geriatric and non-geriatric subpopulations.

Overall, there were no significant differences between race, with the incidence of adverse events in whites (9.2%) being similar to those in nonwhites (11.1%). No adverse event occurred in more than one nonwhite subject.

7.5.4 Drug-Disease Interactions

No trial data for Amyvid to Alzheimer's disease interaction is available.

7.5.5 Drug-Drug Interactions

There are no known drug interactions. Patients on or off AD medications tolerated the drug similarly well. Given the very low mass of florbetapir received in a single Amyvid administration and the very rapid clearance of the drug from circulation, alterations in the pharmacodynamics and pharmacokinetics of other commonly prescribed medications are not anticipated.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity study was conducted for Amyvid. The sponsor requested a waiver for carcinogenicity studies and the waiver was granted.

7.6.2 Human Reproduction and Pregnancy Data

There are no data on Amyvid exposure in pregnant or lactating women, including inadvertent exposure during the drug development program. It is not known if Amyvid is excreted in human milk. The sponsor requested a waiver for human reproduction and pregnancy, and the waiver was granted.

7.6.3 Pediatrics and Assessment of Effects on Growth

There are no data on Amyvid use in pediatric subjects. The sponsor requested a waiver for the assessment of safety and effectiveness of the drug in pediatric patients. The waiver was granted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

1. Overdose: since the drug is given in a controlled situation as a single-dose bolus, it is not expected to have overdose potential.
2. Drug abuse potential: since the drug is given in a controlled situation as a single-dose bolus, it is not expected to have potential for drug abuse.
3. Withdrawal and rebound: since the drug is given in a controlled situation as a single-dose bolus, it is not expected to have potential for withdrawal or rebound effects.

7.7 Additional Submissions

None

8 Postmarket Experience

Since the drug has not been marketed anywhere, there is no postmarketing data available.

9 Appendices

9.1 Literature Review/References

1. CFR 21 Part 315 Diagnostic radiopharmaceuticals 2009 http://law.justia.com/us/cfr/title21/21-5.0.1.1.5.html

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12. CFR 21 part 361.1 Radioactive drug for certain research uses 2009 http://law.justia.com/us/cfr/title21/21-5.0.1.1.29.html

13. Review Classification Policy: Priority (P) and Standard (S), MAPP 6020.3, CDER, FDA. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082000.pdf

14. Huang, SC. Anatomy of SUV. Nuc Med & Biol 27 (7): 643-646, 2000 http://www.ncbi.nlm.nih.gov/pubmed/11091106

15. FDA Guidance for Industry Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs 2005 http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf

9.2 Labeling Recommendations

Concerns regarding the proposed label include the following:

1. There is a significant attempt [redacted] (b) (4) in the label, which might mislead clinicians and patients. All the promotional verbal descriptions, tables and graphs in the label should be eliminated.
2. More detailed reader training information should be incorporated in the label to help the clinician use the drug.

The review will compare other approved PLR labels in the same class for consistency when the drug is considered as approvable.

9.3 Advisory Committee Meeting

A meeting of the Peripheral and Central Nervous System Drugs Advisory Committee was held on January 20, 2011 to discuss the new drug application (NDA) 202-008, Florbetapir F 18 Injection, sponsored by Avid Radiopharmaceuticals.

Questions to the Committee:

1. (Discussion: New Considerations) In 2008, the PCNS Drugs Advisory Committee concluded that "a negative amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer's Disease." Before turning to consider Amyvid™ specifically, discuss any new scientific and clinical developments since 2008 that bear on the clinical utility of a reliable imaging assessment "for the detection of cerebral amyloid."

Committee Discussion: *The committee members felt there have been major advances, especially in mild cognitive impairment (MCI) patients. There was a general consensus that there has been additional scientific research since 2008 which is supportive of the prior recommendations on the clinical utility of a negative scan for amyloid in patients with symptoms consistent with dementia.. Additionally, the committee agreed that the new research offers a stronger evidentiary base for the recommendations from the 2008 advisory committee meeting. The committee was informed by the sponsor that the proposed indication had changed during the review cycle to state that, "Florbetapir F18 injection is a diagnostic radiopharmaceutical indicated for positron emission tomography (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." Certain committee members expressed the opinion that a negative amyloid test may not necessarily rule out amyloid presence but simply make amyloid presence less likely.*

2. (Discussion: Image Read Methods) Two Amyvid™ image reading methods were used in the phase 3 trial (A07): a semi-quantitative scoring method (0 – 4) in the "autopsy" cohort and a "binary" (positive/negative) method in the "specificity" cohort. Only the binary method is proposed for the clinical use of Amyvid™. Discuss the strengths and limitations of the A07 trial data. Consider the following questions:

   a. To what extent would reinterpretation of the A07 "autopsy" cohort images help allay any concern about the lack of binary read results for patients with a histopathological measure of amyloid?

Committee Discussion: *The committee members concurred that the reinterpretation of the A07 autopsy cohort images by a number of readers who use a binary read method would be important for addressing concerns regarding the lack of data and also help address concerns regarding consistency among readers, particularly if the readers use the clinically applicable training methods .*

   b. How important is the establishment of a clinically relevant histopathological "threshold" for determining whether an image is positive/negative?

Committee Discussion: *The committee members agreed that a threshold must be chosen, but voiced concerns that the binary read method and the training in this method needs to minimize the potential for false positives and false negatives as well as inconsistency between image interpretations due to insufficient training. There was general consensus that there is a need for a clinically relevant histopathological "threshold" for determining whether an image is positive/negative.*

   c. How important is the establishment of a clinically-applicable reader training program?

Committee Discussion: *The committee members agreed that it is essential for there to be a clinically-applicable reader training program. Multiple committee members emphasized the*

need to verify the sufficiency of the reader training methods. Members generally did not favor a certification-type approach to the training procedures.

d. How important is the establishment of acceptable reader-to-reader reproducibility for the binary read method, based upon readers trained according to a clinically-applicable training program?

Committee Discussion: *The committee members agreed that it is essential for there to be acceptable reader-to-reader reproducibility for the binary read method, based upon readers trained according to a clinically-applicable training program.*

3. (Discussion: Clinical Population) A phase 2 trial (A05) enrolled healthy control subjects as well as patients with a diagnosis of mild cognitive impairment or Alzheimer's Disease. However, the phase 2 data raise questions about the reader-to-reader reproducibility of the binary read imaging results. Discuss the strengths and limitations of the A05 data. Consider the following questions:

a. To what extent does the A05 population exemplify patients who may ultimately undergo Amyvid™ imaging?

Committee Discussion: *The committee members agreed that the A05 population better exemplifies patients who may ultimately undergo Amyvid imaging.*

b. To what extent would reinterpretation of the A05 images provide useful information, especially if the reinterpretation was performed by readers trained according to a clinically-applicable reader training program?

Committee Discussion: *There was a general consensus that reinterpretation of the A05 images will assess reproducibility of image interpretation among readers, and could increase confidence*

in the readings. The committee members agreed that there is important information to be gained in understanding the consistency of reads utilizing the scans of the A05 patients as a database.

4. (Vote) Do the available data support the approval of Amyvid™ at the present time? Discuss the basis for the vote, including any database deficiencies and ways to resolve these deficiencies (such as the collection of new premarketing or postmarketing data).

   YES: 3 NO: 13 ABSTAIN: 0

Committee Discussion: *The committee members agreed that Amyvid does what it purports to do: That is, it allows for amyloid imaging. However, they voiced concerns regarding the inconsistency in the PET scan readings and the other deficiencies as outlined above. Thus, the committee encouraged FDA to review additional data resulting from implementation and testing of a reader training program aimed at improving reader consistency.*

5. (Vote) If there were implementation of a training program that demonstrated accurate diagnosis within the autopsy standard/population and a demonstration of a reader consistency in the population of intended application such as exemplified by A05, would the available data support the approval of Amyvid?

   YES: 16 NO: 0 ABSTAIN: 0

Committee Discussion: *The majority of the committee members requested the addition of this fifth question so that they may voice their desire to see Amyvid approved contingent upon additional data and resolution of the reader training method concerns. The committee unanimously agreed that the available data support the approval of Amyvid if there were implementation of a training program that demonstrated accurate diagnosis within the autopsy standard/population (A07) and a demonstration of reader consistency in the population of intended application as exemplified by A05. In particular, they recommended that the sponsor*

provide additional data on inter-rater reliability (re-reading of the A07 and A05 scans using the binary method) prior to approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QI FENG
02/11/2011

LUCIE L YANG
02/11/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neurology Products (HFD – 120)
Center for Drug Evaluation and Research

Date: November 15, 2010

From: Russell G. Katz, M.D.
Division Director

Subject: NDA 202008
AMYVID™
Florbetapir F 18 Injection

To: Director
Division of Medical Imaging Products

Document Type: Consult

Enclosed is the Division's response to your request

Review and Evaluation of Clinical Data

NDA (Serial Number)	**202008**
Sponsor:	**Avid Radiopharmaceuticals**
Drug:	**AMYVID (Florbetapir F 18) Injection**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Original NDA/Consult**
Correspondence Date:	**9/17/10**
Date Received By Reviewer:	**10/4/10**
Date Review Completed:	**11/15/10**
Reviewer:	**Nicholas A. Kozauer, M.D.**

1. Introduction

This submission, an original New Drug Application (NDA), has been received as a consultation from the Division of Medical Imaging Products (DMIP).

This NDA seeks approval for Florbetapir F 18 Injection, which is a Positron Emission Tomography (PET) imaging ligand designed to image β-amyloid aggregates in the brain. Specifically, the sponsor seeks the following indication:

"*Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β-amyloid, a defining pathology of Alzheimer's disease (AD)".*

In this consultation request, the primary reviewing division asks the Division of Neurology Products (DNP) to comment on the sufficiency of the data included in the submission to support the proposed indication.

This application has been granted Priority Review status, as sought by the sponsor.

Of note, the use of *in vivo* imaging of β-amyloid using PET as a means of diagnosing Alzheimer's Disease was discussed at a meeting of the Agency's Peripheral and Central Nervous System Drugs Advisory Committee held on October 23, 2008.

Florbetapir F 18 Injection has been developed under IND 79511 and was the subject of a pre-NDA Meeting held on July 13, 2010. The DNP was involved in that meeting, as well as with several other previous submissions for the IND. From the Division's perspective, this NDA submission is in-line with agreements reached at the pre-NDA meeting.

2. Contents of Consultation

This consultation package contains the following components:

- Consultation request
- NDA 202008 in electronic Common Technical Document (e-CTD) format.

3. Contents of Review

In accordance with the consultation request, this review will be confined to a description and discussion of the efficacy data that is provided in favor of Florbetapir F 18 Injection. Please note that no attempt has, however, been made by this reviewer to independently confirm the results of the sponsor's efficacy analyses using the statistical datasets supplied by the sponsor; that task has been entirely deferred to the Agency Biometrics reviewer for this application.

Safety data for Florbetapir F 18 will not be reviewed, as that is also beyond the scope of this consultation.

The contents of the submission will be reviewed under the following principal headings, and in the same order as below:

- Key conclusions at Advisory Committee Meeting (October 23, 2008)
- Currently proposed indication
- Outline of pertinent efficacy data
    - Pivotal Study ^{18}F-AV-45-07
    - Supportive evidence
    - Sponsor's main conclusions regarding efficacy data
- Reviewer's summary comments
- Conclusions

4. Key Conclusions at Advisory Committee Meeting

As noted previously, the use of *in vivo* imaging of β-amyloid using positron emission tomography as a means of diagnosing Alzheimer's Disease was discussed at a meeting of the Agency's Peripheral and Central Nervous System Drugs Advisory Committee held on October 23, 2008.

Florbetapir F 18 was one of three putative amyloid-binding radioligands which were discussed at this meeting.

The following are key extracts copied from the official minutes of the meeting.

Issue: On October 23, 2008, the committee discussed the clinical development of radionuclide imaging products for the detection of amyloid to assist in the diagnosis of Alzheimer's Disease.

Questions to the Committee:

1. To what extent, if any, would an indication for the use of an *in vivo* diagnostic radiopharmaceutical agent for the "detection of cerebral amyloid" provide useful clinical information?

   Committee Discussion:

The committee discussed question #2 first before it discussed question #1. The committee agreed that a" negative" amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer's Disease (AD). Additionally, the committee noted that a" positive" test would have very limited utility since cerebral amyloid is known to be present in multiple conditions, including normal aging. Hence, the clinical usefulness of a "positive" amyloid test was regarded as tenuous. Some committee members noted that a "positive" test might ultimately be useful to help characterize AD, but not to diagnose it. The committee agreed that such a test would probably be a powerful tool for future research. (See Transcript for Complete Discussion)

2. If an *in vivo* diagnostic radiopharmaceutical is clinically useful in the "detection of cerebral amyloid," what should be a "standard of truth" in phase 3 clinical studies?

   Committee Discussion:
   The committee discussed this question first, before question #1. In regards to the indication of detecting amyloid in the brain, the committee overwhelmingly agreed that histopathological correlation should be the "standard of truth" in phase 3 clinical studies. There was discussion about the feasibility of obtaining "enough" pathological studies or the ability to follow study patients to autopsy. A few committee members noted that [11C]PIB may also be a standard of truth; however, other committee members expressed concern that [11C]PIB is not an FDA-approved product and data are insufficient to establish its reliability as a marker for cerebral amyloid. (See Transcript for Complete Discussion)

3. Please comment on the strengths and weaknesses of the phase 3 study outlines supplied by the companies.

   Committee Discussion:
   The committee did not discuss this question specifically since it was agreed upon by the Review Division and the committee that the strengths and weaknesses of the phase 3 study outlines were addressed during the earlier discussions for questions #1 and #2. (See Transcript for Complete Discussion).

5. Currently Proposed Indication

The sponsor's currently proposed indication, as stated in the submission, is as follows:

"*Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β-amyloid, a defining pathology of Alzheimer's disease (AD)".*

The sponsor believes that this proposal is consistent with previous guidance and recommendations from the Agency and the October 23, 2008 Advisory Committee Meeting.

6. Outline of Pertinent Efficacy Data

The sponsor contends that the following four lines of evidence establish the relationship between amyloid burden, as measured *in vivo* with the Florbetapir-PET scan image, and the underlying true amyloid burden (standard-of-truth) determined by postmortem histopathology:

- Florbetapir-PET signal correlates to amyloid histopathology present at autopsy
- Florbetapir-PET scans are negative in subjects without amyloid pathology
- Florbetapir-PET results correlate with known clinical and epidemiological risk factors for brain amyloid
- Florbetapir binds avidly and specifically to brain amyloid *in vitro* and *ex vivo*

The pivotal trial (Study ^{18}F-AV-45-A07) will be reviewed in the most detail as this study provides the majority of the evidence in favor of the sponsor's first two lines of evidence. Data regarding a proposed correlation with known clinical and epidemiological risk factors will also be addressed.

An assessment of the adequacy of the non-clinical studies conducted in support of the sponsor's final line of reasoning is beyond the scope of this consultation and will not be addressed.

6.1 Pivotal Study ^{18}F-AV-45-07

6.1.1 Title

A Phase III Study of the Correlation Between Florpiramine F 18 (^{18}F-AV-45) PET Imaging and Amyloid Pathology

6.1.2 Primary Objective

To test the relationship between measurements of amyloid using Florbetapir F 18 positron emission tomographic imaging and true levels of amyloid burden as determined by histopathology at autopsy.

The study tested the following two primary hypotheses:

<u>Primary hypothesis #1: Correlation analysis:</u>
There is a statistically significant correlation ($\rho>0$) between the semi-quantitative visual rating of amyloid burden of the florbetapir-PET scan and the cortical amyloid burden at autopsy as assessed by quantitative immunohistochemistry (IHC). Spearman's Rank Order Correlation, one-sided, $p < 0.05$, $\rho>0$, was used to assess a significant correlation.

<u>Primary hypothesis #2: Specificity analysis:</u>
The observed specificity of florbetapir-PET imaging is ≥90% in young healthy controls (i.e., ≥90% of the florbetapir-PET scans from subjects in the specificity cohort would be rated as negative).

6.1.3 Design, Dose, Sample Size, and Duration

Between February 2009 and March 2010 the study enrolled 226 subjects across the following two cohorts:

- The autopsy cohort which consisted of 152 subjects from various end-of-life and late-life populations who consented to Florbetapir 18 F-PET imaging and a post-mortem brain autopsy

  The first 6 subjects to come to autopsy were considered "front runners," and an interim analysis was completed on these subjects to finalize the study methods (ultimately, no significant changes were made).

  Three independent imaging physicians evaluated all of the Florbetapir-PET scans in randomized blinded fashion. The neuropathology analyses were independently performed and were blinded to any clinical information, image data, or reading results.

- The non-autopsy or specificity cohort which consisted of 74 young cognitively healthy volunteers, less than 40 years of age, who had no first degree relatives diagnosed with AD.

All patients underwent positron emission tomography of the brain after a single dose (10 mCi; 370 MBq) of ^{18}F-AV-45.

Subjects were imaged at 23 imaging sites using clinical PET and PET/CT scanners, which had been prequalified and standardized using a Hoffman brain phantom and quality control (QC) procedure.

6.1.4 Key Inclusion Criteria

6.1.4.1 Autopsy Cohort

- The enrolling physician's assessment that the subject had a ≤ 6 month life expectancy
- The absence of any known destructive lesions in the brain
- The subject's willingness to have a Florbetapir PET scan and a brain autopsy at the time of death

6.1.4.2 Non-Autopsy Cohort

- Male or female
- ≤ 40 years old
- No known risk factors for Alzheimer's Disease, including

  - Known genetic risk (ApoE genotype is to be determined after enrollment; *those carrying an ApoE ε4 allele will be excluded*)
  - First degree relative with a known progressive dementing disorder
  - History of neurological, neurodegenerative, or psychiatric disease
  - History of head trauma
  - Evidence of brain abnormality on MRI

- Performance within an age-appropriate normal range on psychometric testing (Mini-Mental Status Examination, Wechsler Logical Memory I and II Story A, verbal fluency, orientation, and constructional praxis/clock draw)

6.1.5 Analytic Methods

6.1.5.1 Florbetapir-PET Analysis

For the autopsy Cohort:

- Florbetapir-PET images were assessed visually using a semi-quantitative score ranging from 0 (no amyloid) to 4 (high levels of cortical amyloid) by three board-certified nuclear medicine physicians whose only prior experience with Florbetapir-PET scans occurred during a half-day training session

- The median rating of the readers served as a primary outcome variable

- Readers were blinded to clinical, demographic, and neuropathological information

For the non-autopsy cohort:

- The Florbetapir-PET images were mixed in random order with 40 images from the autopsy cohort blinded read that had (previously) received a median visual read score between 2 and 4 (inclusive)

- The blinded read for the non-autopsy cohort was performed by a *different* group of three independent readers and images were rated as either “amyloid positive” or “amyloid negative”

- The majority view of the three raters was the primary outcome variable for the specificity analysis

A quantitative analysis of the ratio of cortical to cerebellar signal, the Standard Uptake Value Ratio (SUVR), was also performed for Florbetapir-PET images for all subjects participating in the study.

6.1.5.2 Autopsy Analysis

- At the time of death, the brain was removed following standard autopsy procedures and placed in fixative for 2 weeks prior to dissection by an experienced neuropathologist

- Two independent laboratories carried out two different methods to identify and quantify β-amyloid pathology: immunohistochemistry (IHC) using the β-amyloid antibody 4G8; and neuritic plaque density using a Bielschowsky silver stain (to calculate a modified CERAD score)

  The Aβ burden is defined by IHC as the percentage of area in the measurement field occupied by reaction product.

- Average density for both neuritic and diffuse plaques was summarized by anatomical region using a 4-point semi-quantitative scale (0=none, 1=sparse, 2=moderate, 3=severe).

- In addition, a neuropathological diagnosis was made using standardized criteria (CERAD and NIA-Reagan).

6.1.5.3 Statistical Analysis

6.1.5.3.1 Primary Efficacy Analyses

Correlation Analysis (Autopsy Cohort):
The primary hypothesis was that there was a significant positive correlation between the visual semi-quantitative rating of the Florbetapir-PET images (median of three readers) and the quantitative measurements of cortical amyloid burden (IHC). Spearman's rank order correlation was determined as well as the asymptotic standard error (ASE) and 95% confidence interval (CI) using Fisher z-transformation. The associated test (one-sided test, $\rho>0$) was performed with a significance level of $\alpha=0.05$ to assess a significant correlation.

Specificity Analysis (Specificity Cohort):
The primary hypothesis was that the observed specificity of the Florbetapir-PET imaging in the specificity cohort would be ≥ 90% (i.e., ≥ 90% of the Florbetapir-PET scans from subjects in the specificity cohort would be rated as Aβ(-) on an independent read, using the majority view of three readers). For the majority view of the three readers, the number and percent (specificity) of an Aβ(-) Florbetapir-PET scan was determined as well as the 95% CI.

6.1.5.3.2 Secondary Efficacy Analyses

The hypothesis for these analyses was that in each region there would be a significant correlation between the visual semi-quantitative rating of the Florbetapir-PET images (median of three readers) and the quantitative measurements of cortical amyloid burden (IHC). For each of the six brain regions (anterior cingulate, frontal cortex, parietal cortex, posterior cingulate, precuneus, and temporal cortex), Spearman's rank order correlation, the ASE, and 95% CI were determined using Fisher z-transformation. The associated test (one-sided test, $\rho>0$) was performed with a significance level of $\alpha=0.05$ to assess a significant correlation.

6.1.5.3.3 Pre-Specified Exploratory Efficacy Analyses

Spearman's rank order correlation, the ASE, and 95% CI were determined using the Fisher z-transformation for the following exploratory analyses:

- Correlation analysis between the visual semi-quantitative rating of Florbetapir-PET images and cortical neuritic plaque density (modified CERAD score)
- Correlation analysis between quantitative assessment of Florbetapir-PET SUVR and measurement of cortical amyloid burden (IHC)
- Correlation analysis between quantitative assessment of Florbetapir-PET SUVR and the cortical neuritic plaque density (modified CERAD score)
- Correlation analysis between quantitative assessment of Florbetapir-PET SUVR and the visual semi-quantitative rating of Florbetapir-PET images
- Correlation analysis between the visual semi-quantitative rating of Florbetapir-PET images and modified CERAD diagnosis

The associated test for all (one-sided test, $\rho>0$) was performed with a significance level of $\alpha=0.05$ to assess a significant correlation.

6.1.5.3.4 Sample Size Determination

Assuming a true correlation of 0.55, a sample size of 29 subjects with PET scan and autopsy had 90% power to detect a significant positive correlation between the global semi-quantitative rating of amyloid burden (0-4) on the independent read of the Florbetapir-PET scan and the overall cortical amyloid burden at autopsy as assessed by quantitative immunohistochemistry (Spearman's Rank Order Correlation test, $p < 0.05$, $\rho>0$).

For the specificity analysis, with an observed (target) specificity of 90%, a sample size of 40 was required to yield 95% confidence interval (CI) bounds of 80% to 98% (normal approximation).

6.1.6 Outcome Measures

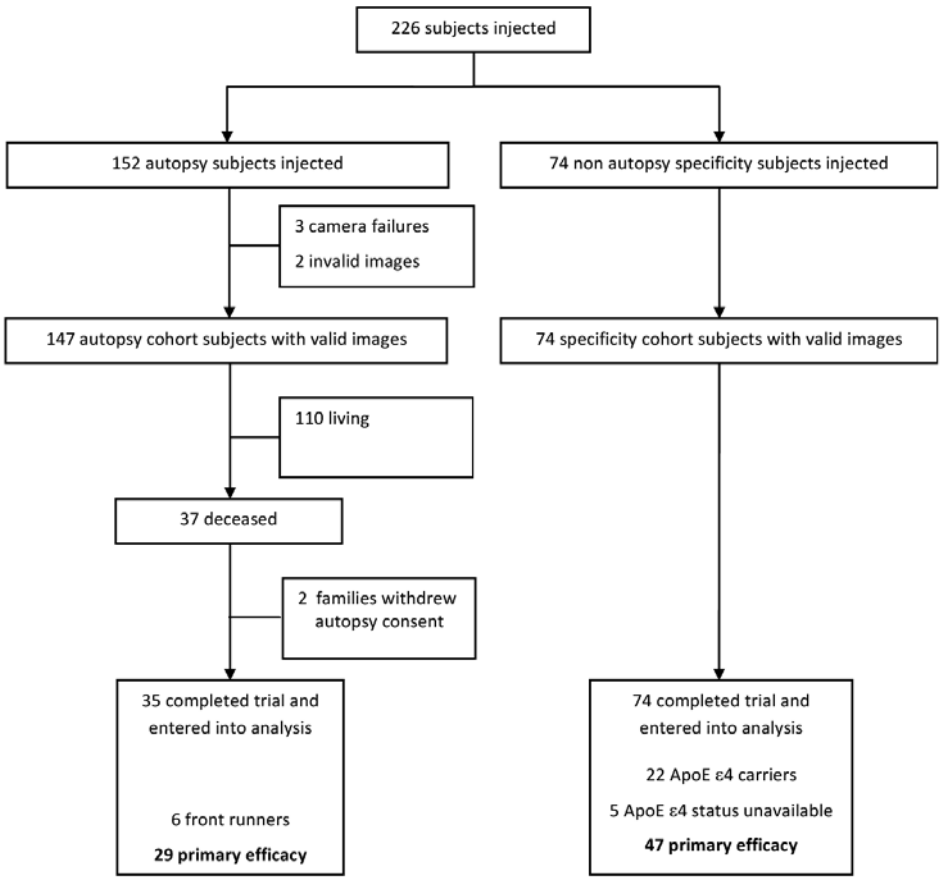
The study had the following <u>co-primary</u> hypotheses:

- There would be a significant positive correlation between the semi-quantitative rating of β-amyloid on the Florbetapir-PET scan (median of three readers) and the average cortical amyloid burden, as determined by immunohistochemistry in the autopsy cohort
- That ≥ 90% of the subjects in the non-autopsy cohort would have a Florbetapir-PET image that was rated as β-amyloid negative.

6.1.7 Results

6.1.7.1 Subject Disposition

The following graphic, copied from the submission, illustrates the status of the initial 226 subjects:



6.1.7.2 Demographics and Baseline Characteristics:

The following graphics, copied from the submission, illustrate the demographic and baseline characteristics for the study populations:

Table 11-2 Demographic Characteristics by Cohort

Characteristic	Autopsy Cohort		Specificity Cohort	
	Subjects Imaged N=152 [a]	Subjects with Autopsy N=29 [b]	Subjects Imaged N=74 [a]	Non-ApoE ε4 Carriers N=47 [b]
Age (years)				
Mean ± SD	78.1 ± 13.35	80.0 ± 13.19	26.6 ± 6.50	26.3 ± 7.17
Median	81.5	85.0	25.5	24.0
Range	38 to 103	55 to 103	18 to 50	18 to 50
Gender				
Male	71 (46.7%)	15 (51.7%)	48 (64.9%)	32 (68.1%)
Female	81 (53.3%)	14 (48.3%)	26 (35.1%)	15 (31.9%)
Race				
Caucasian	134 (88.2%)	26 (89.7%)	57 (77.0%)	36 (76.6%)
Black or African-American	10 (6.6%)	2 (6.9%)	6 (8.1%)	4 (8.5%)
Other	4 (2.6%)	1 (3.4%)	7 (9.5%)	4 (8.5%)
Asian	2 (1.3%)	0	4 (5.4%)	3 (6.4%)
Native American / Alaskan Native	2 (1.3%)	0	0	0
Ethnicity				
Non-Hispanic or Latino	139 (91.4%)	28 (96.6%)	69 (93.2%)	44 (93.6%)
Hispanic or Latino	13 (8.6%)	1 (3.4%)	5 (6.8%)	3 (6.4%)

Source: Supportive Tables 14.1.2.1, 14.1.2.2, and Listings 16.2.3, 16.2.4.6.1, 16.2.4.6.2, 16.2.4.7, 16.2.5

Abbreviations: SD = standard deviation

Percentages were calculated using the number of non-missing values in each cohort.

a) Safety population

b) Primary efficacy population

Table 11-3 Baseline Characteristics by Cohort

Characteristic	Autopsy Cohort		Specificity Cohort	
	Subjects Imaged N=152 [a]	Subjects with Autopsy N=29 [b]	Subjects Imaged N=74 [a]	Non-ApoE ε4 Carriers N=47 [b]
Diagnosis				
Alzheimer's disease	56 (36.8%)	13 (44.8%)	0	0
Mild cognitive impairment	25 (16.4%)	2 (6.9%)	0	0
Other dementing disorder	21 (13.8%)	5 (17.2%)	0	0
No cognitive impairment	50 (32.9%)	9 (31.0%)	74 (100.0%)	47 (100.0%)
MMSE				
N	115	21	74	47
Mean ± SD	21.2 ± 9.34	19.9 ± 9.96	29.7 ± 0.57	29.8 ± 0.40
Median	25.0	23.0	30.0	30.0
Range	0 to 30	0 to 30	27 to 30	29 to 30
Wechsler memory scale –immediate recall				
N	107	19	74	47
Mean ± SD	6.3 ± 5.03	5.9 ± 5.18	16.1 ± 3.34	16.3 ± 2.64
Median	6.0	6.0	16.0	16.0
Range	0 to 19	0 to 17	6 to 23	12 to 22
Wechsler memory scale – delayed recall				
N	107	19	74	47
Mean ± SD	5.1 ± 4.82	3.8 ± 4.50	15.4 ± 3.46	15.4 ± 2.84
Median	5.0	1.0	15.0	15.0
Range	0 to 23	0 to 13	5 to 22	8 to 21
Interval between PET scan and death (months)				
Mean ± SD	--	3.2 ± 2.57	--	--
Interval between death and autopsy (hours)				
Mean ± SD	--	10.7 ± 7.95	--	--

Source: Supportive Tables 14.1.2.1, 14.1.2.2, 14.1.3.3, and 14.1.3.4, and Listings 16.2.3, 16.2.4.4, 16.2.4.6.1, 16.2.4.6.2, 16.2.4.7, and 16.2.5

Abbreviations: MMSE: Mini-Mental State Examination, SD = standard deviation

a) Safety population

b) Primary efficacy population

Although the focus of the analysis was the correlation between imaging and histopathology, it is reassuring that an adequate number of clinically diagnosed AD subjects were included in the autopsy cohort (13). In these subjects, the mean duration from the onset of AD symptoms was 105.9 months (± 46.05) and the mean time from AD diagnosis was 73.2 months representing a fairly advanced disease population as would be expected in a hospice setting.

The time intervals between both scanning and death (3.2 ± 2.57 months) and death and autopsy (10.7 ± 7.95 hours) appear sufficiently short to allow for a meaningful interpretation of the results in the autopsy cohort.

The majority of subjects in both cohorts were Caucasian. There is no consistent evidence in the literature, however, that levels of brain β-amyloid would be expected to differ between races. More importantly, there is also no suggestion that the pathophysiological properties of β-amyloid would be expected to differ between races; therefore there would be no reason to suspect a differing binding profile of the Florbetapir F 18 PET ligand in Caucasians. As such, this imbalance should not affect either the interpretability or generalizability of these findings.

6.1.7.3 Protocol Deviations

The following table, copied from the submission, illustrates all of the protocol deviations in the study:

Table 10-3 Protocol Deviations: All Subjects

	Autopsy Cohort N=152		Specificity Cohort N=74	
Description of Protocol Deviation	**n**	**Subject Number**	**n**	**Subject Number**
Physician not present pre- and post-dose	0	--	11	145-009, 145-010, 145-011, 145-012, 145-013, 145-014, 145-015, 145-016, 145-017, 145-018, 145-020
Wechsler immediate recall score was below study criterion	0	--	3	144-001, 144-009, 271-027
Wechsler immediate and delayed recall scores were below study criteria	0	--	2	321-012, 321-014
MMSE, Wechsler immediate and delayed recall scores were below study criteria	0	--	2	321-007, 321-015
PET scan started significantly more than 80 minutes post-injection	1	054-012	1	062-012
Brain removed more than 24 hours after death	1	059-003	0	--
Subject died more than 1 year after florbetapir-PET imaging	1	134-001	0	--
Subject received a radiation treatment the day before florbetapir-PET imaging	1	062-001	0	--
Subject could not tolerate the 10-minute PET scan	1	060-010	0	--
Subject had hepatitis C	1	064-001	0	--
Subject did not meet inclusion criterion, 18 to 40 years old	0	--	1	140-003
Wechsler delayed recall score was below study criterion	0	--	1	321-013

It does not appear that these deviations would be expected to have a significant effect on the overall outcome or interpretation of the study.

6.1.7.4 Efficacy Results

The following table, copied from the submission, illustrates the respective study populations for analysis:

	Autopsy Cohort	Specificity Cohort
Safety population	152	74
Primary efficacy population	29	47
Efficacy population including Front Runners / ApoE 4 carriers	35[a]	74[b]

a) Includes 6 front runners

b) Includes 27 subjects with ApoE4 gene (or ApoE genotype not available)

6.1.7.4.1 Histopathology Correlation Analysis (Autopsy Cohort)

Among the 35 autopsy cases that were completed as part of the protocol, the final neuropathological diagnoses were:

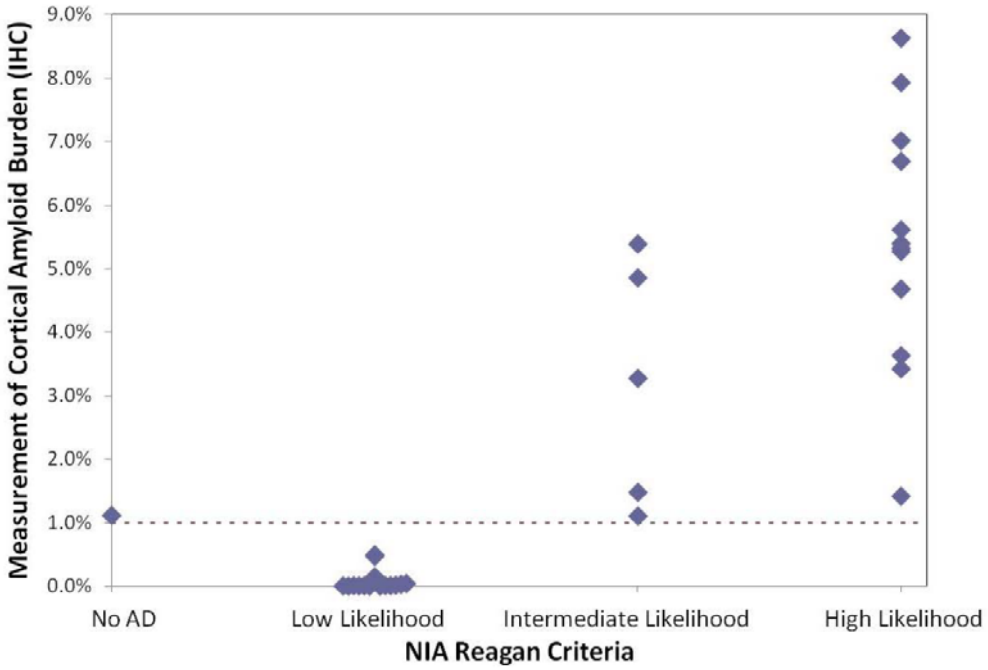
- 19 subjects were diagnosed with AD
- 16 subjects were diagnosed as not having AD

There was 100% agreement between both the CERAD (probable or definite-AD) and the NIA-Reagan (intermediate or high-probability of AD) diagnoses as illustrated in the following graphic, copied from the submission:

Modified CERAD Criteria (Plaques)	NIA-Reagan AD Likelihood				Totals
	No AD	Low	Intermediate	High	
No AD (None)	1	13	0	0	14
Possible (Sparse)	0	2	0	0	2
Probable (Moderate)	0	0	4	0	4
Definite (Frequent)	0	0	1	14	15
Totals	1	15	5	14	35

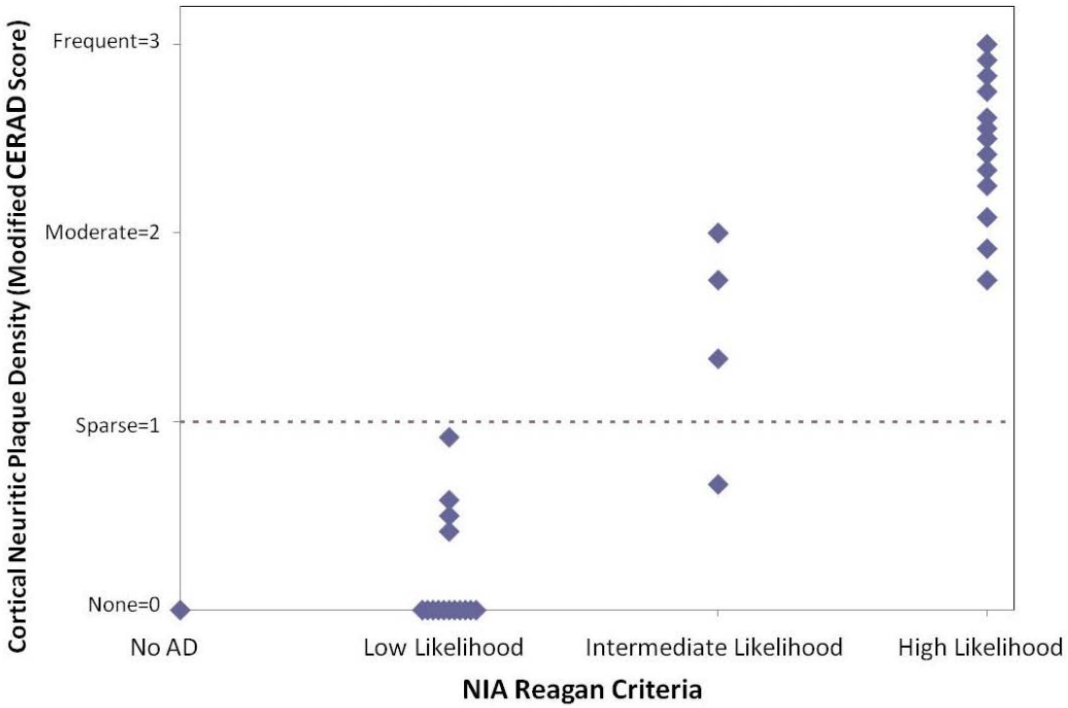
The following are additional key findings from the histopathology correlation analysis:

- A cut-off value of 1% in terms of the IHC amyloid burden, yielded the best separation between neuropathologic cases of AD and those without AD (based on NIA-Reagan criteria) as illustrated by the following figure, copied from the submission:

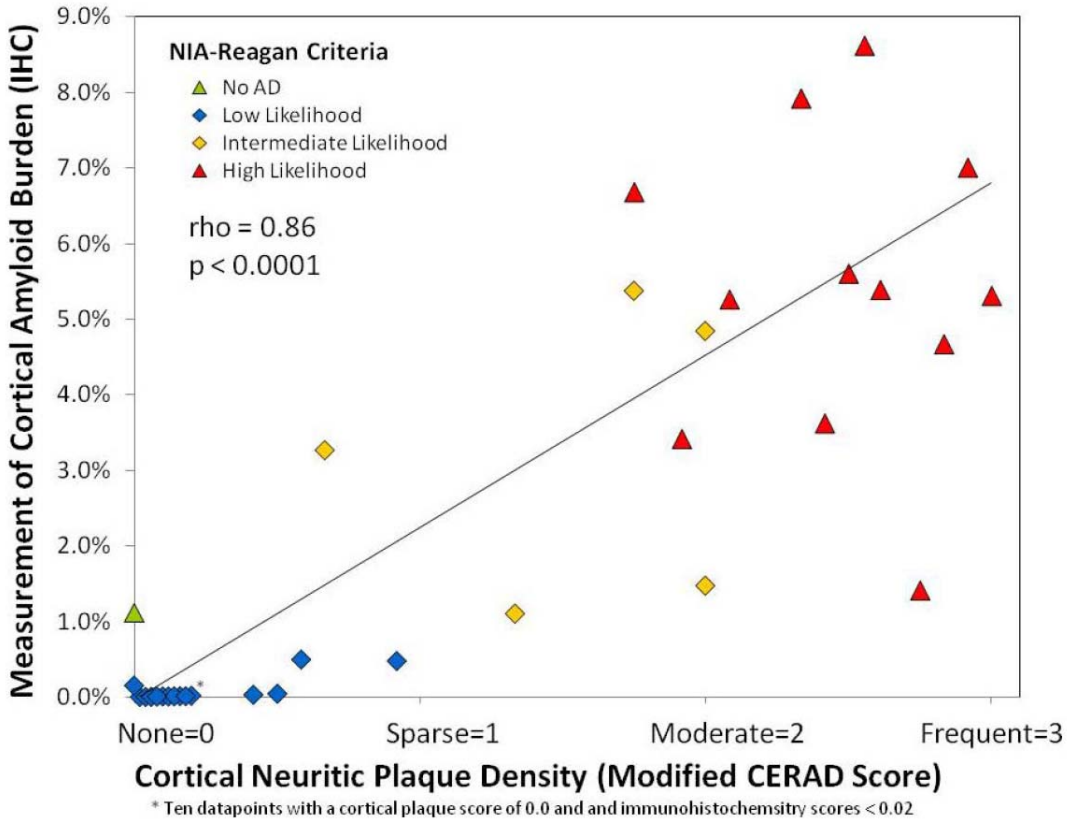


- An arbitrary CERAD cut-off of 1.0 (sparse cortical neuritic plaque density) yielded the best separation between neuropathologic cases of AD and those without AD

(based on NIA-Reagan criteria) as illustrated by the following figured, copied from the submission:



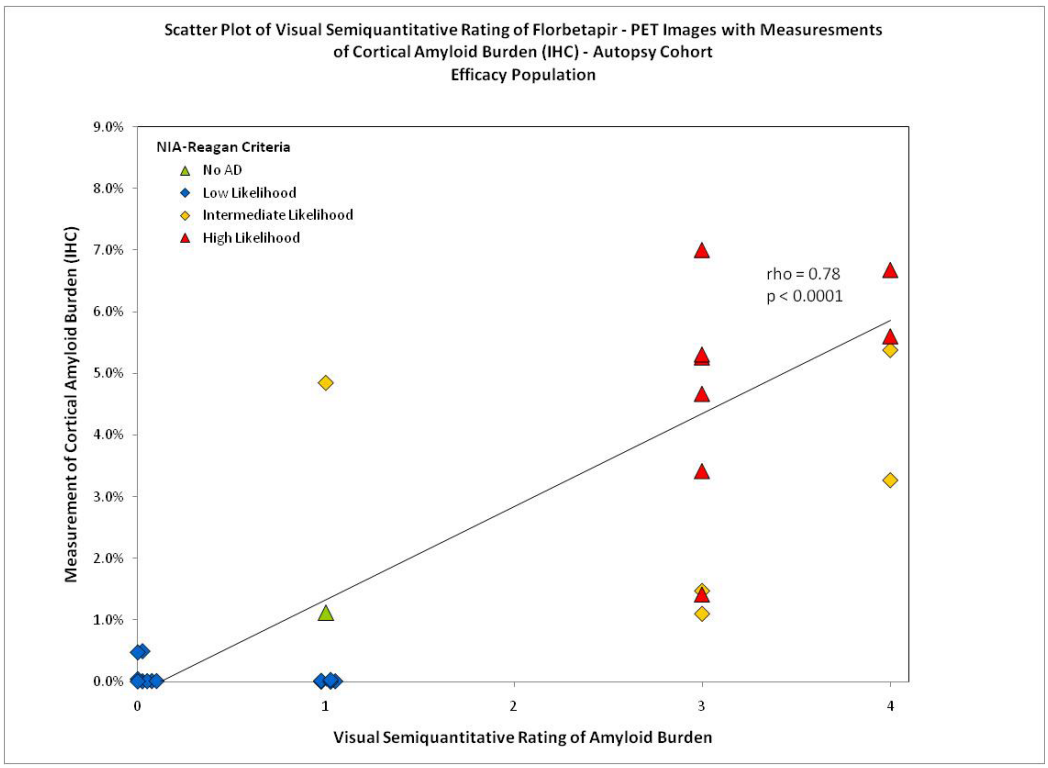
- The was a high degree of correlation between the IHC rating of amyloid burden and the amyloid burden which was calculated based on the modified CERAD (silver staining) score, suggesting that these two post-mortem measures of amyloid burden are similar ($\rho=0.86$, $p<0.0001$) as illustrated by the following figure, copied from the submission:



6.1.7.4.2 Primary Efficacy Analysis

6.1.7.4.2.1 Co-Primary Efficacy Endpoint: Primary Correlation Analysis

The following graphic, copied from the submission, illustrates the correlation between the visual semi-quantitative rating of amyloid burden on Florbetapir-PET scan and amyloid burden measured by IHC at autopsy (excluding the initial 6 so-called “front-runner” cases):



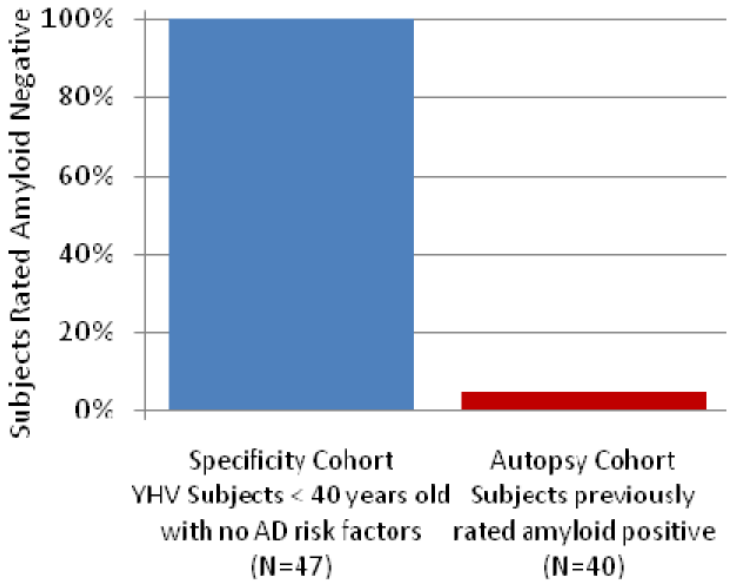
As the figure indicates, an apparently strong and statistically significant correlation Spearman's rho (ρ = 0.78, *P* < 0.0001; 95% Confidence Interval [CI], 0.58 to 0.89) was observed between the semiquantitative visual rating of β-amyloid levels on the Florbetapir-PET image and the cortical β-amyloid levels as assessed by quantitative IHC post-mortem.

The findings were similar when the front-runner cases were included in the analysis, with both results being highly statistically significant.

These results support a strong correlation between the visual semi-quantitative brain amyloid burden, as demonstrated by Florbetapir-PET scanning, and post-mortem amyloid burden measured by IHC.

6.1.7.4.2.2 Co-Primary Efficacy Endpoint: Primary Specificity Analysis

100% (47/47) of the YHC subjects had a negative Florbetapir F 18-PET reading as illustrated by the following graphic, copied from the submission:



The 95% CI for the primary specificity analysis blinded read was 91% to 100%. Thus, the study met its primary endpoint as ≥ 90% of the Florbetapir-PET scans from subjects in the specificity cohort were rated as Aβ(-) on an independent read, using the majority view of three readers.

On a pre-specified exploratory basis, the results were unchanged if all of the young healthy control subjects from the specificity cohort were used: 100% (74/74) with a 95% CI of 94% to 100%.

6.1.7.4.3 Secondary Endpoint: Regional Correlation Analysis of Semi-Quantitative Visual Blinded Read with Measurement of Cortical Amyloid Burden (IHC)

The following table, copied from the submission, illustrates the correlation between the median blinded visual read of the Florbetapir-PET images for each neuroanatomical region and the respective β-amyloid level as assessed by quantitative IHC:

	Efficacy Population		Efficacy Population plus Front-runners	
Region	**Correlation (Spearman's ρ) N=29**	**95% Confidence Interval N=29**	**Correlation (Spearman's ρ) N=35**	**95% Confidence Interval N=35**
Precuneus	0.75	0.53 to 0.88	0.77	0.58 to 0.88
Parietal cortex	0.77	0.56 to 0.88	0.78	0.60 to 0.88
Frontal cortex	0.69	0.44 to 0.84	0.71	0.50 to 0.85
Temporal cortex	0.68	0.42 to 0.84	0.70	0.48 to 0.84
Posterior Cingulate	0.70	0.44 to 0.85	0.71	0.50 to 0.85
Anterior Cingulate	0.74	0.51 to 0.87	0.76	0.57 to 0.87

All results in this table were significant at the $p < 0.0001$ level.

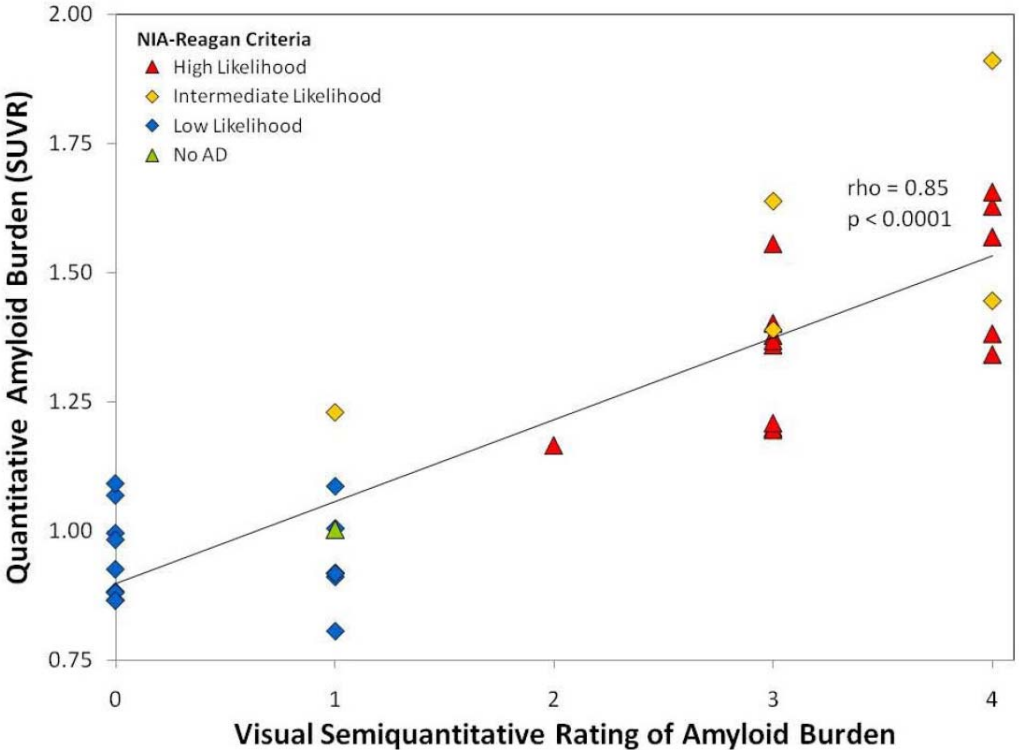
6.1.7.4.4 Exploratory Endpoints

- The correlation between the median blinded visual read of the Florbetapir-PET images and the neuritic plaque density measured using modified CERAD scoring revealed a strong significant Spearman's ρ of 0.71 (95% CI: 0.47 to 0.86, p<0.0001). The results were similar when the front runner cases were added to the primary efficacy population with a ρ of 0.73 (95% CI: 0.52 to 0.85, p<0.0001).

- The correlation between the SUVR assessment of Florbetapir-PET images and the measurements of amyloid burden (IHC) revealed a strong significant Spearman's ρ of 0.75 (95% CI: 0.53 to 0.88, p<0.0001). The results were similar when the front runner cases were added to the primary efficacy population with a ρ of 0.76 (95% CI: 0.56 to 0.87, p<0.0001).

- The correlation between the quantitative SUVR assessment of Florbetapir-PET images and the neuritic plaque density measured using modified CERAD scoring revealed a strong significant Spearman's ρ of 0.74 (95% CI: 0.51 to 0.87, p<0.0001). The results were similar when the front runner cases were added to the primary efficacy population with a ρ of 0.74 (95% CI: 0.54 to 0.86, p<0.0001).

- The correlation between the semi-automated computerized quantitative SUVR assessment of Florbetapir-PET images and the blinded visual read of the Florbetapir-PET images revealed a strong significant Spearman's ρ of 0.82 (95% CI: 0.64 to 0.91, p<0.0001). The results were similar when the front runner cases were added to the primary efficacy population with a ρ of 0.85 (95% CI: 0.72 to 0.92, p<0.0001). These results are further illustrated by the following diagram, copied from the submission:



6.1.7.4.5 Diagnostic Agreement Analysis

6.1.7.4.5.1 Autopsy Cohort

The following tables, copied from the submission, illustrate the diagnostic agreement between the semi-quantitative blinded read and SUVR analysis versus the pathology reference standard in the autopsy cohort:

		Reference Standard: NIA-Reagan		
Florbetapir-PET Image Outcome:		Positive (Intermediate, High) (N=19)	Negative (No AD, Low) (N=16)	
Semi-quantitative Visual Blinded Read	Positive (2,3,4)	18	0	PPV = 100%
	Negative (0,1)	1	16	NPV = 94%
		Sensitivity = 95%	Specificity = 100%	Accuracy = 97%

		Reference Standard: NIA-Reagan		
Florbetapir-PET Image Outcome:		Positive (Intermediate, High) (N=19)	Negative (No AD, Low) (N=16)	
Quantitative SUVR	Positive (≥1.10)	19	0	PPV = 100%
	Negative (<1.10)	0	16	NPV = 100%
		Sensitivity = 100%	Specificity = 100%	Accuracy = 100%

The following are the notable results from this analysis:

- Of the 19 autopsy confirmed cases of AD in the autopsy cohort, 18 had scans which were read as visually positive (median read ≥ 2) resulting in a **sensitivity of 95% (CI: 72%-98%)**
- All 19 scans were read as positive by the automated measure (SUVR > 1.1) resulting in a **sensitivity of 100% (CI: 71%-100%)**
- Of the 16 subjects who had a post-mortem exam not consistent with AD, all had a negative Florbetapir F 18-PET resulting in a **specificity of 100% (CI: 76%-100%)**
- In total, the blinded visual read of the Florbetapir F 18-PET agreed with the final neuropathologic diagnosis in 34/35 cases yielding a **negative predictive value (NPV) of 94% and a positive predictive value (PPV) of 100%**

6.1.7.4.5.2 Specificity Cohort

The following figures, copied from the submission, present the diagnostic agreement tables for the qualitative PET scan read using the presumed amyloid load status as the reference standard in the specificity analysis population:

Florbetapir-PET Image Outcome:		Reference Standard: Presumed Amyloid Status: Positive (Autopsy Cohort[a]) (N=40)	Reference Standard: Presumed Amyloid Status: Negative (Young, Healthy Controls[b]) (N=47)	
Qualitative Visual Blinded Read	Positive (Aβ+)	38	0	PPV = 100%
	Negative (Aβ-)	2	47	NPV = 96%
		Sensitivity = 95%	Specificity = 100%	Accuracy = 100%

Florbetapir-PET Image Outcome:		Reference Standard: Presumed Amyloid Status: Positive (Autopsy Cohort[a]) (N=40)	Reference Standard: Presumed Amyloid Status: Negative (Young, Healthy Controls[b]) (N=47)	
Quantitative SUVR	Positive (≥1.10)	38	0	PPV = 100%
	Negative (<1.10)	2	47	NPV = 96%
		Sensitivity = 95%	Specificity = 100%	Accuracy = 100%

[a]These subjects were randomly selected cases previously read as positive, they were not autopsy-verified to be positive for amyloid.
[b] These subjects were all young healthy, cognitively intact individuals presumed to be amyloid negative

Overall, 95% (38/40) of the images from the amyloid scan positive subjects (from the autopsy cohort) were also read as positive in the specificity analysis (by a separate rating panel)

Additional Results from the Specificity Cohort

- Even with the inclusion of the APOE4 positive YHC control subjects in the analysis, 74/74 were rated as PET negative for amyloid

6.1.7.4.6 Blinded Rater Agreement Analysis

The following tables, copied from the submission, illustrate the blinded inter-rater agreement for the respective cohorts:

Table 11-10 Observed Agreement Between Readers – Autopsy Cohort Efficacy Population

	N	Observed Agreement*	Kappa Statistic
Reader 1 vs. Reader 2	29	91%	0.72
Reader 1 vs. Reader 3	29	95%	0.84
Reader 2 vs. Reader 3	29	91%	0.68

Table 11-11 Observed Agreement Between Readers – Specificity Cohort

	N	Observed Agreement*	Kappa Statistic
Reader 4 vs. Reader 5	114	94%	0.86
Reader 4 vs. Reader 6	114	99%	0.98
Reader 5 vs. Reader 6	114	93%	0.84

As part of the study's design, 40 images were also read by two sets of blinded readers (i.e., first during the autopsy cohort read session, and again mixed randomly with images from the specificity cohort). The overall agreement between the median reads from two blinded reading sessions of the same images was 38/40 (95%).

The following tables, copied from the submission, illustrate the individual reader correlations for the respective cohorts:

Table 11-12 Individual Reader Correlations in the Autopsy Cohort, Primary Efficacy Population

	N	Correlation Between Visual Semi-quantitative Read and IHC Spearman's ρ (CI)	p-value
Reader 1	29	0.73 (0.49 to 0.86)	<0.0001
Reader 2	29	0.81 (0.64 to 0.91)	<0.0001
Reader 3	29	0.65 (0.37 to 0.82)	<0.0001

Table 11-13 Specificity Analysis Performance of Individual Reader – Specificity Cohort

	N	Specificity % (CI)
Reader 4	47	100% (90.6% to 100%)
Reader 5	47	97.9% (87.3% to 99.9%)
Reader 6	47	100% (90.6% to 100%)

6.1.7.4.7 Comparison to Clinical Diagnosis

On an exploratory basis, clinical diagnosis was compared to the neuropathologic diagnosis at autopsy. Of the 23 subjects in the autopsy cohort who had dementia diagnoses in-life (AD or other dementias), 3 subjects (13%) had a clinical diagnosis that did not match the final autopsy diagnosis: a single subject had a diagnosis of probable AD in-life, but was negative for AD at autopsy; and 2 subjects had a clinical diagnosis of other dementing disorders (one each with Parkinson's disease dementia and Lewy body dementia), but both received a final autopsy diagnosis consistent with AD. In contrast to the clinical diagnosis, the Florbetapir-PET scan agreed with the autopsy diagnosis in all 3 of these cases.

6.1.7.4.8 Multivariate/Stepwise Analysis for Quantitative Assessment

On an exploratory basis, stepwise selection models were used to investigate the contribution of age and ApoE allele to the correlation between the quantitative PET imaging result (cortical average SUVR) and each measure of pathology (IHC, Neuritic Plaque Density, CERAD Diagnosis Score, NIA-Reagan Diagnosis Score). In each case, a significant relationship was found between the neuropathology parameter and SUVR, with no additional significant contribution from age or ApoE allele. For example, in a selection model using age, ApoE, IHC, MMSE and intercept to explain SUVR, only IHC and the intercept were statistically significant explanatory variables and the equation is *SUVR = 1.02 + 0.065 x IHC* (i.e., SUVR = 1.0, when IHC = 0.0% cortical grey matter area, or SUVR = 1.34, when IHC = 5.0%).

6.2 Supportive Evidence

In addition to the pivotal trial results, the sponsor presents data from both Phase I and II trials that attempts to demonstrate a correlation between the Florbetapir-PET image and the following variables which have been previously associated with β-amyloid pathology in the literature

- Clinical diagnosis
- Age
- ApoE genotype
- Cognitive performance parameters

A summary presentation of these results is provided in the following sections of this review. The sponsor's presentation of the supportive data in these tables generally also includes findings from the pivotal trial (^{18}F-AV-45-07) as well.

6.2.1 Clinical Diagnosis

The following table, copied from the submission, illustrates the mean SUVR and percent of scans rated as positive for β-amyloid for each study and each clinical presentation:

Table 17: Mean SUVR (top) and Percentage of Subjects Rated Aβ+ (bottom) Across the Five Efficacy Studies by Clinical Diagnostic Category

	Diagnostic Presentation Group				
Study ID	**AD**	**MCI**	**ODD**	**OHC**	**YHC**
Mean (SD) SUVR					
A01	1.40 (0.148)	—	—	1.02 (0.151)	—
A03	1.71 (0.236)	—	—	1.00 (0.069)	0.97 (0.088)
A04	1.45 (0.255)	—	—	0.99 (0.047)	1.00 (0.063)
A05	1.40 (0.267)	1.20 (0.276)	—	1.05 (0.159)	—
A07	1.35 (0.278)	1.18 (0.286)	1.18 (0.329)	1.05 (0.247)	0.96 (0.043)
A07 Primary Efficacy	1.44 (0.202)	0.97 (0.143)	1.05 (.220)	0.96 (0.70)	—
% Amyloid Positive (read)					
A01	100%	—	—	25%	—
A03	100%	—	—	0%	0%
A04	85.7%	—	—	0%	0%
A05	75.6%	38.3%	—	14.1%	0%
A07	81.5%	20.0%	57.1%	12.5%	0%
A07 Primary Efficacy	92%	0%	40%	0%	—

Abbreviations: AD, Alzheimer's disease; HC, healthy controls; MCI, mild cognitive impairment; ODD, other dementing disorders; OHC, Older Healthy Controls; SD, standard deviation; SUVR, standardized uptake value ratio; YHC, young healthy controls.

The submission makes the following key points regarding this data:

- The findings in Study A05 were all statistically significant, given the sufficient number of subjects in each diagnostic category
- Approximately 85% of AD subjects, 40% of MCI subjects, and 15% of cognitively normal subjects were rated as Aβ(+) using any Florbetapir-PET measure. The observation that 15% of clinically diagnosed probable AD subjects were negative for amyloid matches the expected rate of false-positive diagnosis of AD based on referenced autopsy literature.
- Similarly to the previous observation, the finding that 40% of MCI subjects were amyloid positive by Florbetapir-PET scan is consistent with referenced autopsy literature that shows 33 to 62% of MCI subjects are amyloid positive at post-mortem examination
- Additionally, the observation that 15% of healthy control subjects were rated as amyloid positive by the Florbetapir-PET scan is also consistent with the referenced literature reports that 13 to 45% of apparently cognitively healthy subjects have significant β-amyloid pathology at autopsy

6.2.2 Age

The age-related increasing frequency of β-amyloid positive scans, and the increasing intensity of β-amyloid binding seen with Florbetapir-PET for all studies is illustrated by the following table, copied from the submission:

Table 18: Age-related Differences in Florbetapir-PET Signal in Healthy Control Subjects (top) and AD Patients (bottom) by Study

Parameter	Cognitively Healthy Control Subjects				
	< 50	50 – 59	60 – 69	70 – 79	> 80
No. positive/No. total					
A01	0/0	0/4 (0.0%)	0/2 (0.0%)	0/1 (0.0%)	3/5 (60.0%)
A03	0/6 (0.0%)	0/5 (0.0%)	0/0	0/0	0/0
A04	0/7 (0.0%)	0/3 (0.0%)	0/0	0/0	0/0
A05	0/0	1/19 (5.3%)	2/19 (10.5%)	3/20 (15.0%)	5/20 (25.0%)
A07[a]	0/76 (0.0%)	0/5 (0.0%)	0/17 (0.0%)	1/2 (50.0%)	4/21 (19.0%)
SUVR, mean (SD)					
A01	—	0.947 (0.0357)	0.975 (0.0257)	0.931 (0.0070)	1.120 (0.2025)
A03	0.967 (0.0878)	0.998 (0.0690)	—	—	—
A04	0.996 (0.0627)	0.994 (0.0473)	—	—	—
A05	—	1.004 (0.1133)	1.014 (0.1263)	1.062 (0.1655)	1.121 (0.1958)
A07	0.958 (0.0434)	0.981 (0.0712)	0.977 (0.0747)	1.259 (0.2301	1.106 (0.3354)

Parameter	AD				
	< 50	50 – 59	60 – 69	70 – 79	> 80
No. positive/No. total					
A01	0/0	1/1 (100.0%)	2/2 (100.0%)	4/4 (100.0%)	3/3 (100.0%)
A03	0/0	1/1 (100.0%)	1/1 (100.0%)	5/5 (100.0%)	2/2 (100.0%)
A04	0/0	2/2 (100.0%)	2/3 (66.7%)	6/6 (100.0%)	2/3 (66.7%)
A05	0/0	3/5 (60.0%)	4/4 (100.0%)	15/21 (71.4%)	12/15 (80.0%)
A07	0/0	2/2 (100.0%)	6/7 (85.7%)	10/12 (83.3%)	26/33 (78.8%)
SUVR, mean (SD)					
A01	—	1.315	1.435 (0.1333)	1.403 (0.2357)	1.391 (0.0927)
A03	—	1.719	1.376	1.856 (0.1792)	1.488 (0.0283)
A04	—	1.625 (0.1386)	1.229 (0.2445)	1.464 (0.1199)	1.534 (0.4500)
A05	—	1.329 (0.3311)	1.468 (0.2959)	1.418 (0.2499)	1.386 (0.2771)
A07	—	1.474 (0.1351)	1.294 (0.1760)	1.273 (0.2608)	1.381 (0.3051)

Interestingly, there was no age-related trend in AD subjects specifically, although this may be expected given the presumed relative plateauing of brain β-amyloid deposition in subjects with clinically diagnosable dementia.

6.2.3 ApoE ε4 Allele

The following table, copied from the submission, demonstrates that both the prevalence of positive scans and the mean level of β-amyloid, as measured by Florbetapir-PET SUVR, were generally increased in groups with the ApoE ε4 allele:

Table 19: Florbetapir-PET Signal in ApoE ε4 Carriers and Noncarriers by Study and Presentation

Study	AD		MCI		OHC		Total	
	ApoE4	Non-ApoE4	ApoE4	Non-ApoE4	ApoE4	Non-ApoE4	ApoE4	Non-ApoE4
No. positive/No. total								
A04	6/6 (100.0%)	4/6 (66.7%)	—	—	0/1 (0.0%)	0/1 (0.0%)	6/9 (66.7%)	4/12 (33.3%)
A05	19/21 (90.5%)	10/19 (52.6%)	16/22 (72.7%)	4/33 (12.1%)	3/16 (18.8%)	7/56 (12.5%)	38/59 (64.4%)	21/108 (19.4%)
A07	21/21 (100.0%)	13/18 (72.2%)	0/4 (0.0%)	4/15 (26.7%)	2/3 (66.7%)	1/24 (4.2%)	32/63 (50.8%)	19/108 (17.6%)
SUVR, mean (SD)								
A04	1.478 (0.1834)	1.414 (0.3631)	—	—	1.047	0.956	1.329 (0.2666)	1.198 (0.3364)
A05	1.493 (0.1830)	1.254 (0.2801)	1.387 (0.2726)	1.053 (0.1710)	1.118 (0.1843)	1.036 (0.1508)	1.352 (0.2647)	1.080 (0.2006)
A07	1.510 (0.2770)	1.258 (0.2179)	1.167 (0.3139)	1.219 (0.3298)	1.136 (0.1553)	1.038 (0.2380)	1.214 (0.3287)	1.066 (0.2237)

6.2.4 Cognitive Performance Parameters

The following table, copied from the submission, illustrates the apparent relationship between Florbetapir-PET SUVR and performance on cognitive testing:

Table 20: Correlation of Cognitive Measures with SUVR by Diagnostic Group and Study

Cognitive Test	Diagnosis Group	Parameter	A01 (N = 26)	A03 (N = 20)	A04 (N = 24)	A05 (N = 183)
ADAS	AD	Sample Correlation[a]	0.238	–0.581	–0.036	0.125
		P value	0.2458	0.9479	0.5479	0.2079
		N	11	9	14	45
	HC	Sample Correlation[a]	0.256[b]	NA	NA	0.288
		P value	0.183	NA	NA	0.0051
		N	15	11	10	78
	MCI	Sample Correlation[a]	—	—	—	0.075
		P value	—	—	—	0.2850
		N	—	—	—	60
	TOTAL	Sample Correlation[a]	0.735	—	—	0.459
		P value	< 0.0001	—	—	< 0.0001
		N	26	—	—	183
Wechsler – Immediate Recall	AD	Sample Correlation[a]	–0.189	0.577	0.508	–0.283
		P value	0.2939	0.9466	0.9684	0.0298
		N	11	9	14	45
	HC	Sample Correlation[a]	–0.418	—	—	–0.331
		P value	0.0614	—	—	0.0015
		N	15	—	—	78
	MCI	Sample Correlation[a]	—	—	—	–0.066
		P value	—	—	—	0.3082
		N	—	—	—	60
	TOTAL	Sample Correlation[a]	–0.753	—	—	–0.498
		P value	< 0.0001	—	—	< 0.0001
		N	26	—	—	183
Wechsler – Delayed Recall	AD	Sample Correlation[a]	—	0.391	–0.020	–0.220
		P value	—	0.8439	0.4742	0.0735
		N	—	9	14	45
	HC	Sample Correlation[a]	—	—	—	–0.251
		P value	—	—	—	0.0133
		N	—	—	—	78
	MCI	Sample Correlation[a]	—	—	—	–0.069
		P value	—	—	—	0.3013
		N	—	—	—	60
	TOTAL	Sample Correlation[a]	—	—	—	–0.474
		P value	—	—	—	< 0.0001

[a] Pearson's Correlation
[b] In Table 14.2.7, Clinical Study Report, Study A01, the Spearman's correlation between SUVR and ADAS in the HC group was statistically significant ($\rho = 0.524$, $P = 0.045$).

The submission makes the following key points regarding this data:

- In each clinical study, when clinical presentation groups are collapsed, there is a significant inverse relationship between SUVR and memory function as measured by both the Wechsler Logical Memory Test (WLM) – Delayed Recall (WLM–II), and the Wechsler Logical Memory Test – Immediate Recall (WLM–I).

- There were uniformly positive and significant correlations between SUVR and the Alzheimer's Disease Assessment Scale (ADAS)

- Although these differences are not evident when individual diagnostic groups are analyzed (presumably due to the smaller number of subjects and the fact that the clinical groups themselves are defined by cognitive function) the healthy control subjects in Study A05 did demonstrate the same correlations (all statistically significant) as in the overall subject population.

- The larger number of subjects in Study A05 allowed for additional analyses, including a multivariate analysis, indicating that the Florbetapir-PET signal was significant in predicting cognition changes.

6.3 Sponsor's Main Conclusions Regarding Efficacy Data

The sponsor's main conclusions regarding the efficacy data in support of Florbetapir F 18 may be summarized as follows:

Both primary hypotheses in the pivotal trial (Study A07) were confirmed. Specifically:

1) There was a strong, statistically significant correlation ($\rho = 0.78$, $p < 0.001$) between the rating of β-amyloid levels on an independent read of the Florbetapir-PET scan and the cortical amyloid levels at autopsy, as assessed by IHC for subjects in the Autopsy Cohort.

2) The observed specificity of Florbetapir-PET in YHC was 100%: 47 of 47 of the Florbetapir-PET scans from subjects in the non-Autopsy Cohort were rated as negative. With a sample size of 47 YHC subjects and an observed specificity of 100%, the lower limit of the 95% CI was 91%.

Secondary analyses in the pivotal trial further supported the primary analyses:

3) There was a significant correlation between the estimate of amyloid burden on the Florbetapir-PET images and true amyloid burden measured by histology, regardless of the method of evaluation of the scan PET or the method of postmortem histological assessment.

4) Significant correlations between Florbetapir-PET and histopathology were seen for individual brain regions, as well as for the global cortical average. A binary classification of Florbetapir-PET images and histopathology data (amyloid positive or negative) indicated that Florbetapir-PET had a high sensitivity and specificity relative to postmortem histopathology, regardless of which PET or pathology measurement was considered.

Results from Phase I and II trials support the pivotal trial:

5) The Phase III specificity results were corroborated by similar observations in Phase II trials. Florbetapir-PET images from all 89 YHC (< 50 years of age) studied in all trials were rated as β-amyloid negative (using all 3 rating methodologies explored) further confirming the specificity of florbetapir-PET imaging. Thus, 100% (89 of 89) of images across the development program obtained from YHC less than 50 years of age were rated as amyloid negative.

6) Results from Phase I and Phase II trials consistently indicated that both visual read and semi-automated quantization of Florbetapir-PET scans provided results consistent with parameters known to be associated with increased prevalence of underlying β-amyloid pathology, including disease diagnostic status (eg, AD versus HC), age, ApoE genotype, and cognitive performance.

7. Reviewer's Summary Comments

This submission, an original New Drug Application (NDA), has been received as a consultation from the Division of Medical Imaging Products (DMIP).

This NDA seeks approval for Florbetapir F 18 Injection, which is a Positron Emission Tomography (PET) imaging ligand designed to image β-amyloid aggregates in the brain. Specifically, the sponsor seeks the following indication:

"*Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β-amyloid, a defining pathology of Alzheimer's disease (AD)".*

In this consultation request, the primary reviewing division asks the Division of Neurology Products (DNP) to comment on the sufficiency of the data included in the submission to support the proposed indication.

This application has been granted Priority Review status, as sought by the sponsor.

Of note, the use of *in vivo* imaging of β-amyloid using PET as a means of diagnosing Alzheimer's Disease was discussed at a meeting of the Agency's Peripheral and Central Nervous System Drugs Advisory Committee held on October 23, 2008.

Florbetapir F 18 Injection has been developed under 79511 and was the subject of a pre-NDA Meeting held on July 13, 2010. The DNP was involved in that meeting, as well as on several other previous submissions for the IND.

7.1 Study 18F-AV-45-A07

This is the pivotal study conducted in favor of the approval of Florbetapir F 18 Injection which has attempted to correlate the visual ratings of β-amyloid burden on Florbetapir-F 18-PET with true levels of amyloid burden as determined by histopathological examination at autopsy.

Between February 2009 and March 2010 the study enrolled 226 subjects across the following two cohorts:

- The <u>autopsy cohort</u> which consisted of 152 subjects from various end-of-life and late-life populations who consented to Florbetapir 18 F-PET imaging and a post-mortem brain autopsy

The first 6 subjects to come to autopsy were considered "front runners," and an interim analysis was completed on these subjects to finalize the study methods (ultimately, no significant changes were made).

Three independent imaging physicians evaluated all of the Florbetapir-PET scans in randomized blinded fashion. The neuropathology analyses were independently performed and were blinded to any clinical information, image data or reading results.

- The non-autopsy or specificity cohort which consisted of 74 young cognitively healthy volunteers, less than 40 years of age, who had no first degree relatives diagnosed with AD.

All patients underwent positron emission tomography of the brain after a single dose (10 mCi; 370 MBq) of ^{18}F-AV-45.

Key inclusion criteria for the autopsy cohort were as follows:

- The enrolling physician's assessment that the subject had a ≤ 6 month life expectancy
- The absence of any known destructive lesions in the brain
- The subject's willingness to have a Florbetapir PET scan and a brain autopsy at the time of death

Key inclusion criteria for the specificity cohort were as follows:

- Male or female
- ≤ 40 years old
- No known risk factors for Alzheimer's Disease, including
  - Known genetic risk (ApoE genotype is to be determined after enrollment; *those carrying an ApoE ε4 allele will be excluded*)
  - First degree relative with a known progressive dementing disorder
  - History of neurological, neurodegenerative, or psychiatric disease
  - History of head trauma
  - Evidence of brain abnormality on MRI
- Performance within an age-appropriate normal range on psychometric testing (Mini-Mental Status Examination, Wechsler Logical Memory I and II Story A, verbal fluency, orientation, and constructional praxis/clock draw)

Florbetapir-PET scans were assessed both by a panel of 3 independent raters who received a ½ day training as to how to interpret the scans. The scans were also evaluated quantitatively by SUVR analysis.

Histopathological samples were analyzed by two independent laboratories who identified and quantified β-amyloid pathology by using immunohistochemistry methods (IHC) and a Bielschowsky silver stain (to calculate a modified CERAD score), respectively. In addition, a neuropathological diagnosis was made using standardized criteria (CERAD and NIA-Reagan).

The study has met its pre-defined co-primary endpoints as follows:

- In the autopsy cohort, this study was able to demonstrate a strong statistically significant correlation between the semi-quantitative visual rating of β-amyloid levels on the Florbetapir-PET image and the cortical β-amyloid levels as assessed by quantitative IHC post mortem.

- In the specificity cohort, the 95% CI for the primary specificity analysis blinded read was 91% to 100%. Thus, the study met its primary endpoint as ≥ 90% of the Florbetapir-PET scans from subjects in the specificity cohort were rated as Aβ-negative on an independent read using the majority view of three readers.

Although I will not restate the findings here, the study also was able to demonstrate strong statistical significance in the analysis of all of the secondary and exploratory endpoints. These primarily looked at the correlation of various cross-comparisons of the different outcome measures used in the study.

7.2 Supportive Evidence

The submission presents further additional analyses of their Phase I and II studies that demonstrate a correlation between findings on Florbetapir-PET and clinical diagnosis, age, ApoE genotype, and cognitive performance measures. These findings will not be reproduced again in this summary as they are detailed in Section 6.2 of this review.

7.3 Discussion of Overall Efficacy Results

The pivotal study in this NDA (Protocol ^{18}F-AV-45-A07) provides highly statistically significant findings (all at a $p < 0.001$ level or greater) that support the conclusion that the assessment of brain β-amyloid *in vivo* by Florbetapir-PET imaging demonstrates a strong correlation with the assumed histopathological standard of truth (IHC). This was demonstrated both in an elderly cohort of end-of-life patients who underwent an autopsy as well as in an assumed amyloid negative cohort of young healthy subjects without any discernable AD risk factors.

Additionally, multiple secondary analyses of the data, which primarily have examined various cross-comparisons of alternative methods of assessment (i.e., the automated image analysis using SUVR) all further support the study's primary conclusion at a high degree of statistical significance (also at a $p < 0.001$ level or greater).

Based on a close inspection of the study design and efficacy results, I find little reason to doubt that Florbetapir F 18 Injection provides a sufficiently accurate measurement of brain β-amyloid levels *in vivo* when compared to the assumed histopathological standard-of-truth.

The most obvious potential deficiency in the design of the study in my opinion is the fact that the AD subjects were all advanced in their disease process which might be assumed to make the interpretation of a positive scan easier. This would be particularly relevant in that the most likely presumed clinical implementation for Florbetapir-PET imaging will be in individuals with milder cognitive impairments (that is not to say that the imaging of already somewhat advanced patients should not also be expected to occur, particularly on the initial post-approval availability of the product). I do not, however, find the lack of earlier stage AD patients in the study to present a significant hurdle to its interpretation for the following reasons:

- The study was designed to evaluate the correlation of β-amyloid as determined by Florbetapir-PET and histopathology, not specifically with a diagnosis of AD.

- A substantive amount of clinical literature suggests that levels of β-amyloid in the brain are high even pre-morbidly in AD patients and that these levels, to some degree, have reached a plateau once the disease becomes clinically manifest. The submission also provides the following table which demonstrates that the mean SUVR does not differ significantly when broken down by MMSE performance (data from their Phase I and II studies are also included in this analysis):

	Mild (MMSE > 18)	Moderate (MMSE 10 – 18)	Severe (MMSE < 10)
Study A07, Primary Efficacy Population	1.39[a]	1.56 (0.134)	1.40 (0.194)
ISE Database	1.52 (0.184)	1.51 (0.252)	1.42 (0.229)

[a] Only a single subject in the A07 Primary Efficacy Population with mild AD.

Another concern is that the interpretation of the scans was based on the median of the 3 raters; as opposed to an individual rater as will be the case in clinical practice. However, each individual rater also met their pre-specified success criteria. For each rater there was a statistically significant correlation between the PET amyloid burden as indicated by the semiquantitative read and the true amyloid levels on IHC (0.73, 0.81, 0.64, all p values < 0.001). Similarly, for the qualitative read in the younger control subjects, each rater exceeded the target of 90% specificity (values were 98%, 100%, and 100% with the 3 raters). The sponsor also points out that the blinded readers all had minimal, if any, previous experience with the interpretation of amyloid imaging agents.

7.4 Specific Questions from DMIP

The Division was additionally asked to respond to the following three questions (with the related responses following the respective questions) during the course of this review:

1) Please comment on the accuracy and objectivity of immunohistochemistry versus silver staining for amyloid.

The pivotal Study A07 used the 4G8 immunohistochemical (IHC) stain for β-amyloid which recognizes a region in the middle of the Aβ peptide (residues 17-24) and has been shown to demonstrate mostly amyloid plaques without cores (diffuse or "fleecy" plaques). Alternatively, the modified Bielschowsky silver stain has consistently been shown to label both diffuse and neuritic β-

amyloid plaques as well as neurofibrillary tangles and is a critical component of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) diagnostic criteria for AD.

Ultimately, both methods have been shown to be accepted and reliable, albeit methodologically differing, measures of brain β-amyloid. Further reassuring is the sponsor's secondary correlation analysis showing a high degree of correlation between the IHC rating of amyloid burden and the amyloid burden which was calculated based on the modified CERAD (silver staining) score, suggesting that these two post-mortem measures of amyloid burden are similar ($\rho=0.86$, $p<0.0001$) in Study A07.

2) Please comment on the regional differences in cortical amyloid deposition in Alzheimer's Disease.

The deposition of brain β-amyloid has been demonstrated to follow a typical pattern of progression in AD. A generally accepted model of this pattern of deposition is the following (Thal DR, *et al. Sci Aging Knowledge Environ (6): 1,* 2006):

- Stage 1: Senile plaque pathology begins with the first diffuse plaques in the neocortex and extends hierarchically into further brain regions;
- Stage 2: Plaques occur in allocortical areas, such as the enterorhinal region, and in the subiculum/CA1 region;
- Stage 3: The basal ganglia, the thalamus, and the hypothalamus become involved
- Stage 4: The midbrain and medulla oblongata become involved
- Stage 5: The pons and the cerebellum become involved

It should be noted that brain amyloid deposition is increasingly thought to have largely plateaued by the onset of clinical dementia. The six brain regions evaluated by the sponsor as part of the secondary analysis (anterior cingulate, frontal cortex, parietal cortex, posterior cingulate, precuneus, and temporal cortex) are all neocortical regions known to be affected in AD by Stage 2 of this model at the latest.

3) Please comment on conditions in which there is amyloid deposition in the cerebellum and the relationship of cerebellar deposition to cortical deposition of amyloid.

Cerebellar amyloid deposition can occur in the later stages of AD. In these cases however, Aβ most frequently localizes to the external molecular layer and has generally not been seen in either the dentate nucleus or other cerebellar nuclei. The nature of the amyloid found in the cerebellum tends to be more amorphous than the aggregated, fibrillar deposits found in the cortex and striatum and typically are not associated with reactive neuritis or glial cells. As a result, these diffuse plaques are typically not visualized by standard histochemical stains such as H&E or Congo Red (Joachim CL *et al., Am J of Pathol 135(2):309-319, 1989*).

Cerebral amyloid angiopathy (CAA) describes the accumulation of leptomenigeal and cortical vessel amyloid and results from a variety of both familial (rare) and sporadic clinical conditions. Sporadic CAA is associated with aging and is a common feature of AD although no clear correlation exists between the distribution of brain CAA and senile plaques. Outside of the context of AD, CAA has also been shown to result in lobar and less frequently cerebellar amyloid deposition and lead to lobar and cerebellar hemorrhage, leukencephalopathy, small cortical ischemic infarcts, and plaque deposition. That said, cerebellar amyloid deposition is a relatively rare finding in sporadic CAA.

To the best of our knowledge, isolated cases of cerebellar amyloid deposition (without cortical involvement) have not been demonstrated (Zhan R *et al., J Zhejiang SCI 5(10):1262-1269, 2004*).

Of note, it is unclear to this reviewer the extent to which the lack of MRI image co-localization would affect the interpretation/visualization of amyloid in the cerebellum with Florbetapir F 18.

7.5 Application in Clinical Practice

There are several potential concerns which I believe are worth anticipating with regard to the application of Florbetapir-PET in clinical practice.

First, it is unclear to me based on a review of the submission including the "Guidance for Image Interpreters" section of the sponsor's proposed draft labeling, as to exactly what information will be conveyed to an ordering clinician in a given individual Florbetapir-PET scan report. In other words, will the scan simply be read as β-amyloid positive or negative or will the ordering clinician also be provided information on the semi-quantitative (visual read score) and/or quantitative (SUVR) assessment as well?

Secondly, irrespective of the fact that the sponsor is seeking an indication to "rule out" AD in the presence of a negative scan, there will no doubt be an inherent (and likely unavoidable) temptation by ordering clinicians in the field (not to mention patients and caregivers) to view a positive scan as supportive of an Alzheimer's diagnosis as this is the natural (although incorrect and/or unproven) converse interpretation.

Thirdly, there are several ongoing efforts by leading organizations and researchers in the Alzheimer's Disease field that are seeking to define patients at increasingly earlier stages of disease such as the "prodromal or preclinical AD" stage including the NIA-Alzheimer's Association Diagnostic Criteria Working Groups and International Working Group for New Research Criteria for the Diagnosis of AD (Dubois Criteria). It should be clear that these criteria have not been validated yet in the field, much less recognized by the Agency at this point. Nonetheless, these various criteria for prodromal AD generally include the co-occurrence of mild cognitive deficits along with a positive biomarker, for which a positive amyloid PET scan image is often used as a primary example. Undoubtedly, as these efforts progress any related proposed criteria will become increasingly publicized (as happened dramatically in the media after the NIA-AA working group criteria were announced at the 2010 International Conference on Alzheimer's Disease meeting, for example). In this context, one can envision a presumably common scenario where a patient who presents with mild cognitive deficits will be subsequently referred for a Florbetapir-PET scan which is read as "positive." Although the strict intent of an approval of the Florbetapir F 18 ligand would only be for a claim to rule-out AD in the setting of a negative scan, this individual would now meet these proposed criteria for

prodromal AD in all likelihood. Despite the current lack of validation of any such diagnosis as prodromal AD, my concern is that this situation might strongly tempt a clinician, particularly a non-specialist, to forgo further work-up of a patient's cognitive complaints. Again, the reaction of a patient and/or caregiver to a positive scan also should be considered, particularly in the absence of any overt dementia syndrome.

As just outlined, there are several inherent potential pitfalls in the interpretation of an individual Florbetapir-PET scan *report* by both ordering clinicians and patients/families despite the assumption of appropriate product labeling with regard to the claims made in the Indications and Usage portion of the Florbetapir F 18 Injection label. Given these concerns, it will be critical to make every effort to reinforce an understanding in the community (through the use of promotional materials and other available means) that the benefit of a Florbetapir-PET scan is strictly with respect to **ruling out** AD in the setting of a negative scan.

It would be ideal to include some form of a qualifying statement on all Florbetapir-PET image reports clearly and specifically indicating that the test is not approved to detect or diagnose Alzheimer's Disease although I recognize that this may be beyond the purview of the Agency's authority.

8. Conclusions

In the estimation of this reviewer, the data presented **does** provide sufficient evidence that Florbetapir-PET accurately images the presence of β-amyloid *in vivo.* As such, I would recommend approval of Florbetapir-PET for the sponsor's desired indication:

"*Florbetapir F 18 Injection is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β-amyloid, a defining pathology of Alzheimer's disease (AD)".*

Being able to rule-out the presence of β-amyloid *in the context* of a comprehensive clinical assessment would provide a useful diagnostic tool that is not currently available otherwise.

I would strongly urge that appropriate safe-guards are considered through both labeling and other measures, to the extent allowable by Federal regulations, to temper what I would expect will be the natural tendency of many clinicians and families to interpret a positive scan as favoring a diagnosis of Alzheimer's Disease (or some form of prodromal Alzheimer's Disease) which has not been demonstrated and would explicitly not be the intent of an approval.

Addendum 1:

Based on an internal discussion at the Mid-Cycle Review meeting held on November 18, 2010, the following additional analyses were completed with regard to the inter-rater agreement for the full autopsy cohort.

The following analysis examines the inter-rater agreement for the semi-quantitative image rating of β-amyloid load (0-4) in the entire autopsy safety cohort who had valid PET images (147 subjects).

It should be noted that according to the submission, it appears that a rating of 0 or 1 would be considered a "negative" scan while a rating of 2, 3, or 4 would be considered a "positive" scan.

The following key findings can be made from an analysis of this data:

- There was complete rater agreement (all 3 raters gave identical ratings for a given image) in only 33/147 images (22%). In 28 of the 33 images for which there was complete agreement the rating was either all a 0 (23 images) or all a 4 (5 images)

- The following differences were observed between the highest and lowest ratings for a given scan (i.e., if one reader rated a scan a 3 and another rated the same scan a 1 this was considered a difference of 2)

    - Difference of 2: 22 images (15%)
    - Difference of 3: 26 images (18%)
    - Difference of 4: 3 images (2%)

  The total number of scans where the difference between the high and low readings was equal to or greater than 2 therefore was 51 (37%)

- More concerning is the fact that in 50 of the 147 (34%) images there was a difference in the interpretation between the readers that would have led to alternate clinical categorizations of a scan being deemed either "positive" or "negative." [i.e., One reader rated a scan either a 0 or 1 (considered to be amyloid negative) and at least one of the 2 other readers rated the same scan a 2, 3, or 4 (considered to be amyloid positive].

- Strikingly, in 16 of the images a scan was rated as having a global amyloid load of 0 by at least one reader and a high rating of either a 2 (6 images), 3 (7 images), or a 4 (3 images).

Conclusions:

- The amount of reader disagreement is concerning in and of itself but it is particularly troubling that a given individual would have had a different final image report as positive or negative depending on the reader in up to 34% of the cases.

- Given that 37% of the images differed by a rating of two or more, the use of the median rating of three readers can be misleading and is not representative of how the scan will be applied clinically.

- In one of their exploratory analyses, the sponsor was able to demonstrate a strong correlation between the quantitative reading of the images (SUVR) and immunohistochemistry (IHC) with a significant Spearman's ρ of 0.75 (95% CI: 0.53 to 0.88, $p < 0.0001$). It seems to this reviewer that given the high rate of inter-reader disagreement, an automated measure of scan interpretation might prove more accurate although it is not in my experience to offer an opinion as to how such a cut-point as to whether an image would be considered positive or negative should be established to ensure acceptable sensitivity and specificity.

- It still appears that the compound itself accurately measures brain amyloid when compared to the IHC standard of truth. What is less clear is to how reliably this can be applied clinically in the currently proposed manner.

- One drawback of these current conclusions is that this relatively high rate of disagreement is based on an analysis of the entire autopsy cohort, regardless of memory complaints. It may be assumed that in clinical practice, where subjects who undergo a Florbetapir-PET scan are likely to present with some sort of memory concern, the occurrence of an entirely negative scan would be presumably much less common and therefore of sufficiently more benefit.

  Nonetheless, there were 16 images where a scan was rated as <u>completely negative</u> (rating of 0) by one reader but as positive by at least one of the readers (a rating of 2, 3, or even a 4). This suggests that the propensity for reader disagreement does not solely exist in cases of subtle distinction (i.e., a rating of a 1 versus a 2, for example) and provides the opportunity for what might be clinically damaging misinterpretations.

- Perhaps a plausible path forward might involve, but certainly not be limited to, one of the following approaches:

  - Further investigating the possible implementation of a quantitative analysis of the images (SUVR) with regard to making a meaningful clinical interpretation

  - Conduct a form of "debriefing" with the previous raters, particularly in the cases where there was marked rating disagreement, to further develop an improved training methodology by discerning the root cause of the errors that might inform a future re-analysis of the scans in a subsequent study

Addendum 2:

The following comments are produced in light of new information that was presented at a face-to-face meeting that was held with the sponsor on 11/23/2010.

This was the third meeting between the sponsor (Avid Radiopharmaceuticals/recently acquired by Eli Lilly and Company) and the Agency since the original submission of the NDA for AMYVID™. The primary intent of this meeting was to clarify how a Florbetapir-PET scan will be interpreted in clinical practice. This process was not made sufficiently clear in the original NDA submission or by the sponsor up to this point to the satisfaction of the primary review division (DMIP).

Prior to the meeting, the sponsor provided the Agency with the following summary points which they intended to address in their meeting presentation and in their newly revised proposed product labeling:

1. Added the recommendation and supportive information for binary (amyloid positive / amyloid negative) image interpretation for use of florbetapir-PET in routine clinical practice.
2. Removed any claim language around AD diagnosis; replaced with information regarding pathology detection based on CERAD plaque scores instead of NIA-Reagan.
3. Added recommendation for training of new users of florbetapir F 18, included instructions with example scans in the PI and provided PI reference to a website (to be prepared by Avid and reviewed with FDA prior to market clearance) for additional sample images and training materials.
4. Revised dosimetry section to reflect potential radiation dose from CT for PET/CT studies.
5. Added recommendations for imaging (timing, positioning, scan parameters used in Phase III).
6. Included recommendation that the scan should be read in the absence of clinical information.

The following were the key summary points that emerged from the meeting:

- The sponsor clarified that the correlation between the PET rating and IHC staining (a continuous variable) would be relied upon to demonstrate the effectiveness of the Florbetapir F18 compound (e.g., it binds amyloid reliably).

- The sponsor further proposed that the clinical reading should be of a <u>binary nature</u> (positive versus negative) as was performed by the raters in the specificity cohort. For this analysis, they proposed that a rating in the specificity cohort of 0-3 should be correlated with the CERAD estimation (which employs the Bielschowsky silver staining method) of amyloid pathology as follows:

Plaque Count	CERAD pathology rating	Correlation to PET rating
0	None	0
1-5	Sparse	1
6-19	Moderate	2
20+	Frequent	3

  A score of 0 or 1 would be equated to a read of “negative” and a score of 2 or 3 (i.e., anything greater than sparse) would be equated with a read of “positive.” It should be noted that the correlation between the CERAD pathology score and the PET rating of 0-3 is simply a proposal by the sponsor to facilitate the numerical analysis of this data and were not part of a pre-specified clinical rating of the scans themselves by the Readers (as these were only read as amyloid-positive or -negative).

- Therefore, the principal dataset that should be relied upon to ascertain the performance characteristics (sensitivity and specificity) ***of the clinical reading*** of a Florbetapir-PET scan should be the complete specificity cohort consisting of 114 total subjects including:

  - 74 younger healthy normal controls (47 of whom were APOE-negative)

  - 40 “amyloid-positive” scans from the sensitivity (autopsy) cohort of which only 14 were confirmed by an autopsy standard of truth. The additional

26 "amyloid-positive" scans originally received a median positive rating (2, 3, or 4) but were not deceased at the time of the analysis and therefore there was no autopsy confirmation of their "positivity" per se.

It should be noted that the 3 readers (Readers 4, 5, and 6) for the specificity cohort were different then the 3 readers from the sensitivity cohort (Readers 1, 2, and 3).

- The sponsor also presented Table 12.2.11.1 from their NDA submission illustrating the correlation between the *median* semi-quantitative visual rating in the autopsy cohort and the semi-quantitative CERAD pathology scores for the 29 autopsy cases included in the primary analysis. The correlation coefficient from this analysis was 0.789 with a SE of 0.194 and a 95% CI between 0.5937 and 0.8961 at a p-value of < 0.0001.

- The sponsor presented the following table, reproduced from the presentation, which demonstrates a high degree of inter-rater agreement with respect to the binary rating in the specificity cohort.

Visual qualitative reading of global amyloid burden	N	Observed agreement	Kappa	SE	95% CI
Reader 4 vs. Reader 5	114	94%	0.8609	0.0509	0.7613, 0.9606
Reader 4 vs. Reader 6	114	99%	0.9801	0.0198	0.9413, 1.000
Reader 5 vs. Reader 6	114	93%	0.8399	0.0545	0.7332, 0.9467

- The sponsor also proposed a training method (preliminary point #3 above) that they suggested could be further validated prior to launch. This proposal raised the question of if this training methodology would be permissible to include in labeling, would this training have to be certified, and how any such inclusion and/or certification would need to be approached from a regulatory standpoint.

Conclusions:
The following conclusions and summary points can be made based on this presentation and the data in general:

1) The sponsor's intended Guidance for Use will rely on clinicians receiving a binary reading of an image as amyloid-positive or amyloid-negative

2) This determination is meant to correlate with the CERAD amyloid pathology score which employs the Bielschowsky silver staining technique (not the final pathological diagnosis) with a score of anything greater than a rating of "sparse" equating to a scan being read as "amyloid-positive"

3) The primary dataset used to base the analysis of performance characteristics of a Florbetapir-PET scan in clinical practice should be the complete specificity cohort of 114 subjects as outlined above

4) Of the 40 scans from the autopsy cohort that were mixed in with the younger subjects scans to comprise the specificity cohort, only 14 actually had an autopsy and were considered to be "amyloid-positive" by this standard of truth. The other

26 scans were included as "amyloid-positive" solely based on the *median* rating of Readers 1, 2, and 3 where a median reading of 2-4 was considered to be positive. However, of these 26 scans, 15 (58%) were rated by at least one reader as having a score of either 0 or 1 which would be considered "amyloid-negative" despite the median rating being "positive."

Therefore, in the opinion of this reviewer, it is inappropriate to included any of these 26 scans in the interpretation of the accuracy of a binary rating in the specificity cohort as these scans are not confirmed by any standard of truth and actually have a high rate of disagreement even between the original 3 readers despite the median being deemed "amyloid-positive."

5) Of the 14 autopsy confirmed positive scans included in the specificity analysis, it is well worth noting that all but one of these subjects were deemed pathologically as having Definite AD based on the modified CERAD criteria (the other subject was deemed as having Probable AD).

6) Therefore, due to the nature of the scans included from the autopsy cohort in the specificity analysis, the Readers were essentially reviewing either scans deemed to be "amyloid-positive" from severely ill elderly patients [with pathologically confirmed advanced (terminal) AD in the case of the 14 scans who had autopsy data] or much younger healthy controls and asked to make a binary decision as to if a scan was positive or negative.

   A serious apparent flaw in this study design is that the Readers could likely tell without much difficulty (and even though they were blinded to any clinical data or the study design) that the scans that they were reviewing were either of younger brains or of elderly ill brains (all of whom were previously considered, or confirmed in the case of the 14, to be amyloid positive). In other words, they were comparing cases of subjects who were either "very positive" or "very negative." Therefore, it is not difficult to assume that a pattern would readily become apparent to a Reader that the scans either fell into a dichotomy of young and negative or elderly and positive thereby even further facilitating the distinction of whether a scan was deemed positive or negative.

   In the opinion of this reviewer the inherent bias (and to a degree unintentional unblinding) in the design of the primary specificity analysis explains the discrepancy between the high rate of reader agreement in the specificity cohort when compared to the relative poor rate of reader agreement in the autopsy cohort (when one looks beyond the median rating). Given this conclusion, it is highly suspect that any conclusions of the performance characteristics of a Florbetapir-PET scan in clinical practice (where the scan will be applied in many more cases that fall into a "gray" area with respect to the amount of amyloid pathology present) can be accurately extrapolated from the specificity analysis where readers essentially made a binary read based on a polarized sample of cases that were either quite positive or quite negative.

7) It would seem that one possible approach to demonstrate reader agreement with respect to a clinically useful binary rating would be to have the complete set of the 35 scans from the autopsy cohort rated by a new set of Readers as either "amyloid positive" or "amyloid negative." I would also see no reason to limit the

number of Readers to three in order to confidently demonstrate inter-rater agreement.

It should be noted that this approach is based on the fundamental premise that the Florbetapir-PET scan accurately images brain amyloid. In this context though, it remains critical that the sponsor can demonstrate that a scan can be reliably interpreted clinically which has not been convincingly shown to this point, despite a high-rate of inter-rater agreement, due to the apparent design flaws in the trial methodology utilized in the analysis of the specificity cohort as outlined above.

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Nicholas A. Kozauer, MD
Medical Reviewer
Division of Neurology Products

_____
Russell Katz, MD
Division Director
Division of Neurology Products

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/s/

NICHOLAS A KOZAUER
01/04/2011

RANJIT B MANI
01/04/2011

RUSSELL G KATZ
01/05/2011