CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202008Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY NDA REVIEW

NDA	202-008
Submission Date	October 7, 2011, SDN 19
Category	Resubmission/Class 2
Brand Name	AMYViD™ [Florbetapir F18 Injection, ^{18}F-AV-45]
Formulation	10-, 30-, or 50-mL multidose vials containing 10 mL, 10-30 mL, or 10-50 mL, respectively, of a clear, colorless solution at a strength of 37 - 1900 MBq/mL (1.0 -50 mCi/mL) Florbetapir F 18 at time of calibration
Route of Administration	Intravenous
Dosing Regimen	Single dose of 10.0 mCi
Indication	The proposed indication is, (b) (4) [redacted]
Applicant	Avid Radiopharmaceuticals, Inc.
Reviewer	Christy S. John, Ph.D.
Team Leader	Gene Williams, Ph.D.
Division Director	NAM Atiqur Rahman, Ph.D.

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1. Executive Summary

The current NDA is a re-submission of NDA 202-008. The original submission received a Complete Response Letter (CRL) from the FDA on March 17, 2011.

A major limitation of the original application was the high inter-reader variability of AMYViD PET scans. The applicant, Avid, designed a reader training program that has resulted in more consistent image interpretation of the scans. No new clinical studies were conducted.

There are no new clinical pharmacology studies in this re-submission. The current review includes review of two articles which were published since the original NDA submission. The first article questions the approval of any of the currently developed beta amyloid binding PET imaging agents (Moghbel et al., Eur J Nucl Med Mol Imaging 39, 202-208, 2012). The second article is a companion article (Villemagne et al., Eur J. Nuc Med Mol Imaging, 39, 209-219, 2012) that agrees with some of the points made in the first article. Based on these articles, the reviewer concludes that the difficulty in reading Florbetapir F 18 PET scans, including the high inter-reader variability, might be a result of non-specific binding.

The high inter-reader variability is especially noteworthy in that it occurred under somewhat idealized circumstances – the readers were experts in the field of brain PET image interpretation. In contrast, radiologists/nuclear medicine physicians with less expertise will be reading the PET images post-marketing. Thus, variability in image interpretation is likely to be even greater post-marketing than it was in the clinical trials.

For these reasons, utilization of standard uptake value ratio (SUVR, an automated semi-quantitative measurement) to improve the accuracy of reads and reduce inter-reader variability should be investigated. We propose a post-marketing requirement (PMR) to investigate SUVR.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V has reviewed the re-submitted NDA 202-008. The submission is acceptable from a clinical pharmacology perspective provided a mutual agreement is reached on labeling.

1.2 Post Marketing Requirements

As noted in the March 17, 2011 FDA Complete Response Letter (CRL) for the original New Drug Application, there is significant inter-reader variability in the interpretation of Florbetapir F 18 PET scans. The inter-reader variability is especially noteworthy in that it occurred under somewhat idealized circumstances – the readers were experts in the field of brain PET image interpretation. In contrast, radiologists/nuclear medicine physicians with less expertise will be reading the PET images post-marketing. Thus, variability in image interpretation is likely to be even greater post-marketing than it was in the clinical trials. For these reasons, utilization of standard uptake value ratio (SUVR, an automated semi-quantitative measurement) to improve the accuracy of reads and reduce inter-reader variability should be investigated. We propose the following (indented) post-marketing requirement (PMR) for approval.

> The applicant will conduct a trial to determine if the use of standard uptake value ratio (SUVR) will increase the accuracy of blinded reads of scans by community hospital radiologist/nuclear medicine physicians. The scans will be obtained in patients with clinically diagnosed Mild Cognitive Impairment (MCI) or Alzheimer's Disease (AD). The trial will include a control group of age-matched healthy volunteers. The primary objective of the trial is to determine if SUVR will improve reading accuracy beyond that which occurs with a visual read alone.

1.3 Summary of Clinical Pharmacology Findings

There are no new clinical pharmacology studies submitted in this resubmission.

During the current review cycle, the group Public Citizen filed a letter with the Agency that questioned the approval of any beta amyloid binding PET imaging agent, including AMYViD. The scientific basis for this petition was a recently published article (Moghbel et al., Eur J Nucl Med Mol Imaging 39, 202-208, 2012). The article includes the following items (paraphrased from the original, indented) that support that non-specific binding contributes significantly to imaging results.

- There is a discrepancy between the distribution of beta amyloid in brain on PET scan with that seen with histopathological and immunohistochemical staining with brain autopsy tissues. Imaging studies with all PET beta amyloid agents have shown preferentially high radioactivity uptake in frontal lobe. In contrast,

autopsies of the brains of AD patients show highest concentrations in occipital and temporal lobes and lower concentrations in frontal lobes.
- PET imaging with beta amyloid agents show significant uptake in white matter, an area known to be completely devoid of amyloid.

The issue of non-specific binding was also noted in a companion article (Villemagne et al., Eur J. Nuc Med Mol Imaging, 39, 209-219, 2012) with multiple authors (prominent researchers in beta amyloid imaging using PET agents), including the inventors of the prototypic beta amyloid imaging agent [^{11}C]PIB (Drs. Chet Mathis and William Klunk). While the authors rebut some of the items in the Moghbel et al., they also somewhat agree with Moghbel et al. regarding non-specific binding. Villemagne et al. write …"the level of this nonspecific white matter retention does not differ between Alzheimer disease (AD) patients and normal controls … . … This non-specific retention continues to represent a challenge to optimizing the analysis of Aß imaging positron emission tomography (PET) data."

The reviewer concludes that the difficulty in reading Florbetapir F 18 PET scans, including the high inter-reader variability, might be a result of non-specific binding.

2. Question-Based Review

For a complete Question-Based Review (QBR) see Appendix 4.2, which is the review of the original (prior) NDA submission.

2.1. General Attributes of Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Avid Radiopharmaceuticals Inc, a fully owned subsidiary of Eli Lilly & Company, has re-submitted New Drug Application 202-008 for AMYViD [Florbetapir F 18 Injection] in response to the FDA Complete Response Letter (CRL) issued on March 17, 2011. A major limitation of the original NDA was the high inter-reader variability in interpretation of the scans. The CRL recommended development of a training program as an attempt to reduce the inter-reader variability in the interpretation of the images. The current submission is a re-read of the original data using readers trained under the training program Avid developed.

The inter-reader variability that resulted in the CRL is especially noteworthy in that it occurred under somewhat idealized circumstances – the readers were experts. As radiologists/nuclear medicine physicians with less expertise will be reading post-marketing, the reading challenges are likely to be even greater post-marketing. For these reasons, the ability of improving reading by utilizing standard uptake value ratio (SUVR, an automated semi-quantitative measurement) to improve the accuracy of reads and reduce inter-reader variability should be investigated. We propose the following (indented) post-marketing requirement (PMR) for approval.

The applicant will conduct a trial to determine if the use of SUVR will increase the accuracy of blinded reads by community hospital radiologist/nuclear medicine physicians in patients with clinically diagnosed Mild Cognitive Impairment (MCI) or Alzheimer's Disease (AD). The trial will include a control group of age-matched healthy volunteers. The primary objective of the trial is to determine if SUVR will improve reading accuracy beyond that which occurs with a visual read alone.

2.1.2 What are the proposed therapeutic indication(s) and mechanism(s) of action?

Avid's proposed indication is,

Avid's proposed mechanism of action includes the following language (indented):

Florbetapir F 18 binds to β-amyloid plaques and the F 18 isotope produces a positron signal that is detected by a PET scanner. Florbetapir F 18 binds with high avidity and selectivity to β-amyloid plaques derived from human brain tissue obtained post-mortem from patients with AD pathology. In equilibrium binding studies using homogenates of AD brain tissue, the dissociation constant for Florbetapir was measured at Kd = 3.7±0.3 nM … .

During the current review cycle, the group Public Citizen filed a letter with the Agency that questioned the approval of any beta amyloid binding PET imaging agent, including AMYViD. The scientific basis for this petition was a recently published article (Moghbel et al., Eur J Nucl Med Mol Imaging 39, 202-208, 2012). The article includes the following items (paraphrased from the original, indented) that support that non-specific binding contributes significantly to imaging results.

- There is a discrepancy between the distribution of beta amyloid in brain on PET scan with that seen with histopathological and immunohistochemical staining with brain autopsy tissues. Imaging studies with all PET beta amyloid agents have shown preferentially high radioactivity uptake in frontal lobe. In contrast, autopsies of the brains of AD patients show highest concentrations in occipital and temporal lobes and lower concentrations in frontal lobes.
- PET imaging with beta amyloid agents show signficant uptake in white matter, an area known to be completely devoid of amyloid.

The issue of non-specific binding was also noted in a companion article (Villemagne et al., Eur J. Nuc Med Mol Imaging, 39, 209-219, 2012) with multiple authors (prominent researchers in beta amyloid imaging using PET agents), including the inventors of the prototypic compound beta amyloid imaging agent [^{11}C]PIB (Drs. Chet Mathis and

William Klunk). The authors state that …"the level of this nonspecific white matter retention does not differ between Alzheimer disease (AD) patients and normal controls … ." … This non-specific retention continues to represent a challenge to optimizing the analysis of Aß imaging positron emission tomography (PET) data."

The reviewer concludes that the difficulty in reading Florbetapir F 18 PET scans, including the high inter-reader variability, might be a result of non-specific binding.

2.2. General Clinical Pharmacology
2.3. Intrinsic Factors
2.4. Extrinsic Factors
2.5. General Biopharmaceutics

For a complete Question-Based Review (QBR) see Appendix 4.2, which is the review of the original (prior) NDA submission.

3. Detailed Labeling Recommendations

The reviewer's proposed edits to the package insert appear as "tracked changes" beginning on the following page. The NDA annotations that appear in the proposed language will, of course, be deleted from the text after the final version is negotiated with Avid. The graph on page 11 of the package insert is a deleted item. It appears as an overlay only because it is a figure of such size that "track changes" does not relocate it to the right hand margin.

35 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix 4.2 Clinical Pharmacology review of the original (prior) NDA submission

95 Page(s) have been Withheld in Full immediately following this page. Please refer to the Original Clinical Pharmacology Review with Submission Date of 9/17/10, by Reviewer Christy S. John, Ph.D., located in this Clinical Pharmacology Section.

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/s/

CHRISTY S JOHN
03/13/2012

GENE M WILLIAMS
03/13/2012

NAM ATIQUR RAHMAN
03/13/2012

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	202-008	**Brand Name**	Amyvid
OCP Division V	V	**Generic Name**	Florbetapir F-18 Injection
Medical Division	Division of Medical Imaging Products	**Drug Class**	Imaging
OCP Reviewer	Christy S. John, Ph.D.	**Indication(s)**	(b) (4)
OCP Team Leader	Gene Williams, Ph.D.	**Dosage Form**	Clear Solution
		Dosing Regimen	370 MBq (10 mCi) of AMYViD is administered as a single intravenous bolus dose in a total volume not exceeding 10 mL.
Date of Submission	10/07/2011	**Route of Administration**	Intravenous Injection
Estimated Due Date of OCP Review	2/15/2012	**Sponsor**	Avid Radiopharmaceuticals, Inc.
PDUFA Due Date	04/07/2012	**Priority Classification**	S

Division Due Date	02/30/2012			
Clin. Pharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**	**5**	**5**	
Tabular Listing of All Human Studies				
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**X**			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:				
Patients-				
single dose:	X			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	**X**			
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				

Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**5**			

Filability and QBR comments

	"X" if yes	**Comments**
Application fileable ?	**X**	This application is resubmission in response to CR letter issued to sponsor in March 2011. There are no new clinical pharmacology studies in this submission. However, a recent publication (M.C. Moghbel et al. Eur J Nuc Med Mol Imaging, Oct 2011) was recently submitted to Agency (by Public Citizen Group) questioning the binding of all beta amyloid radiopharmaceuticals to beta amyloid in brain. This paper and other references cited therein will be reviewed.
Comments sent to firm ?	None	
QBR questions (key issues to be considered)	Does Florbetapir F-18 bind to beta amyloid specifically or not?	
Other comments or information not included above		

Primary reviewer signature	**Christy S. John, Ph.D.**
Secondary reviewer Signature and date	**Gene Williams, Ph.D.**

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

/s/

CHRISTY S JOHN
11/04/2011

GENE M WILLIAMS
11/04/2011

CLINICAL PHARMACOLOGY REVIEW

NDA:	**202-008**
Submission Date:	**September 17, 2010**
Brand Name:	**Amyvid**
Generic Name:	**Flobetapir F-18 injection**
Formulations:	**Sterile solution**
Route of Administration:	**Intravenous injection**
Dosing Regimen:	**10 mCi**
Indication:	**For Positron Emission Tomography (PET) imaging of β-amyloid aggregates in the brain.**
Sponsor:	**Avid Radiopharmaceuticals, Inc.**
Type of Submission:	**Original NDA; 1P**
Relevant IND:	**IND 79,511**
OCP Division:	**DCP-5**
ORM Division:	**DMIP**
Reviewer:	**Christy S. John, Ph.D.**
Team Leader:	**Young Moon Choi, Ph.D.**

Reference ID: 2904801

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1. EXECUTIVE SUMMARY

Florbetapir F-18 is a positron emission tomography (PET) imaging compound. The applicant is seeking the approval of this drug for PET imaging of β-amyloid aggregates in the human brain, specifically, looking for negative scan to rule out the presence of β-amyloid. This drug is the first in the class of β-amyloid PET imaging agent.

To support the approval, the applicant submitted the results of one pivotal Phase 3 study, and six Phase 1 and 2 studies. Clinical pharmacology studies include PK/PD, dosimetry, biodistribution, metabolism, dose-response and test-retest reproducibility of flobetapir F-18 PET imaging. A drug-drug interaction potential was evaluated in vitro using tissue binding study.

Flobetapir F-18 appeared to be distributed to cortical target regions such as precuneus, frontal cortex, and temporal cortex, which are known to have a high density of β-amyloid. Based on the distribution and wash out data, 30 to 50 minutes is recommended for imaging. Florbetapir F-18 is rapidly cleared from circulation post-intravenous injection. The major elimination route is through hepatic metabolism. The metabolites were accumulated in the liver and then excreted with bile juice. For dose selection, a quantitative image assessment, i.e., standard uptake value ratio (SUVR) assessments, and visual ratings of beta-amyloid levels from the PET scans were evaluated after administration of 111 MBq (3mCi) and 370 MBq (10 mCi) doses. Based on the better

Reference ID: 2904801

visual image quality ratings and acceptable radiation dosimetry, a dose of 370 MBq was chosen as the standard dose for clinical application. The test-retest results showed that flobetapir scan was reproducible. The test-retest variability of a quantitative image assessment (SUVR) was less than 5 %. Also there was an agreement between test and retest scans found on the visual read for both the qualitative (amyloid positive or amyloid negative) and semiquantitative (0 to 4) amyloid burden scores.

Any dedicated pharmacokinetic studies in special populations were not performed. However, population analysis of PET scan data showed no difference in florbetapir F 18 binding as a function of gender, race, age or presence of medications, such as namenda and anticholinesterases for the treatment of Alzheimer disease (AD).

Overall, the NDA is acceptable from a clinical pharmacology perspective, and no further studies are necessary.

However, the β-amyloid was found in various levels of cognitive impaired patients including healthy controls. Also the quantitative relationship between the amount of β-amyloid and level of disease is not established. Furthermore, the fundamental scientific question is remained without clear answer, i.e., whether the presence of β-amyloid is a result of certain disease, or the signal of a certain disease, e.g., AD. Therefore, one general concern remained on the proposed qualitative binary read. If the PET diagnosis appeared β-amyloid positive, the expected challengeable questions are 'How much of β-amyloid is there?' and 'How to interpret the positive scan?' In this context, an accurate, objective, and reproducible quantitative read of β-amyloid is desirable.

1.1. RECOMMENDATIONS

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V has reviewed the submission NDA 202-008, and found acceptable from a clinical pharmacology perspective provided that satisfactory agreement is reached between the sponsor and the Agency regarding the language in the package insert.

1.2. PHASE IV COMMITMENTS

None

1.3. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Florbetapir F 18 (formerly known as ^{18}F-AV-45 or florpiramine F 18) is a molecular imaging agent designed for PET imaging of β -amyloid aggregates in the human brain. The proposed indication is for PET imaging of β-amyloid aggregates in the human brain, specifically, looking for negative scan to rule out the presence of β-amyloid.

Reference ID: 2904801

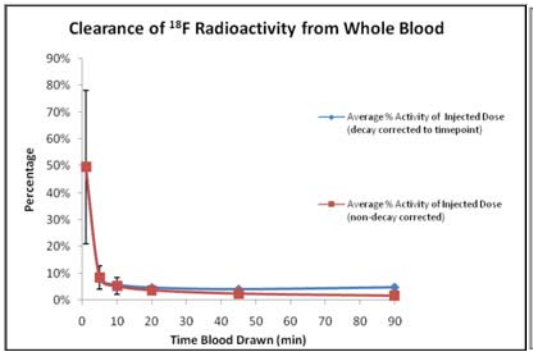
In support of this application, the applicant has conducted a total of seven studies, one pivotal Phase 3 study (Study A07), and six Phase 1 and 2 studies (Study A01 - 06). Among these studies, the review focused on the studies A01 – 06 from clinical pharmacology perspectives. For A07, the clinical pharmacology review focused on the correlation of SUVR with autopsy data.

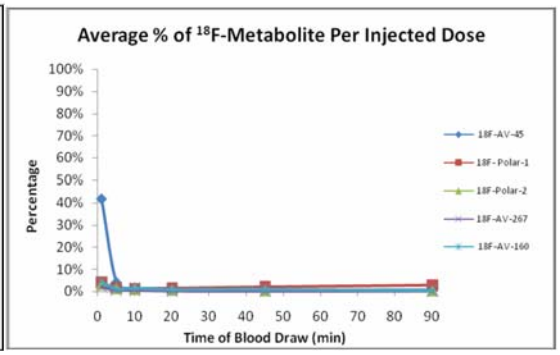
Clinical pharmacology findings are as following:

Biodistribution and Dosimtery

The uptake and time course of brain distribution of florbetapir F-18 was evaluated in Study A01, Study A03, and Study A06. In AD patients, florbetapir F 18 was selectively retained in cortical target regions such as the precuneus, frontal cortex, and temporal cortex, which are known to have a high density of β-amyloid aggregates. The washout of the tracer in healthy control (HC) subjects was sufficiently rapid to allow good visual and quantitative discrimination of HC from AD patients beginning 30 minutes after injection. The correlation between the 2 time points, across all subjects (analyzed in report A06), was nearly perfect (Pearson's $r=0.97$, $p<0.0001$), with the 30 minute SUVR accounting for more than 93% of the variance in the 50 minute SUVR.
Based on these results, an uptake period of 30 to 50 minutes is recommended for clinical application.

The metabolism and clearance of florbetapir F 18 in humans were evaluated in Studies A01 and A03. Florbetapir F 18 is very rapidly cleared from circulation post-intravenous injection. In the principal PK/metabolism study, A03, it was determined that less than 5% of the injected F-18 radioactivity remains in blood by 20 minutes following administration. The residual activity in circulation at that time included low levels of parent florbetapir F 18 (1.2% of initial dose), the desmethyl derivative (AV-160 at 1% of initial dose), and polar metabolites (1.5% of initial dose). By 90 minutes, less than 2% of the injected F-18 remained in circulation and essentially all of the F-18 in circulation at that time was in the form of more polar metabolites of florbetapir F 18.





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Study A02 evaluated the whole body distribution and elimination by means of serial whole body imaging. Rapid brain penetration and washout was observed in normal subjects along with rapid blood clearance. Consistent with other study results suggesting hepatic metabolism, the whole body scans demonstrated rapid accumulation of F-18 in the liver, followed by biliary excretion into the GI tract.

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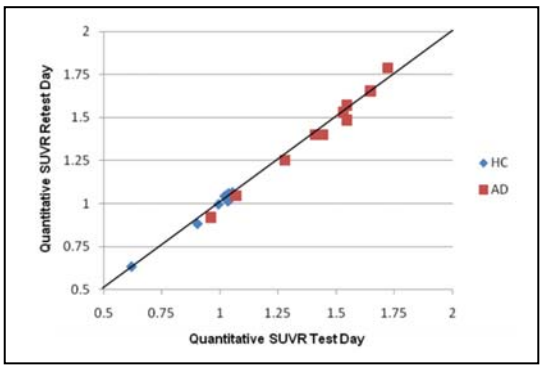
Drug-Drug Interaction Potential

Florbetapir F 18 is administered IV as a single micro-dose, the drug rapidly penetrates the brain and binds avidly to β -amyloid, there is little potential for pharmacokinetic drug-drug interactions. Potential pharmacodynamic drug-drug interactions have been evaluated *in vitro* using tissue binding assays and *in vitro* film autoradiography. None of the commonly prescribed or over-the-counter drugs used by the elderly, which were evaluated, significantly altered florbetapir F 18 binding or autoradiographic labeling of brain tissue from AD patients.

Effective Dose Finding

Study A03 was conducted in part to explore the range of effective doses for florbetapir F 18. Overall, quantitative SUVR assessments and visual interpretation of PET imaging results were similar for subjects given 111 MBq (3 mCi) dose and 370 MBq (10 mCi) dose of florbetapir F 18. However, subjective rating of image quality was better at 370 MBq. Based on these results, a dose of 370 MBq is recommended as the standard dose for clinical application.

Test-Retest Reproducibility



The test–retest reliability of florbetapir-PET imaging was evaluated in Study A04. The florbetapir-PET scan was reproducible (See the Figure). The inter correlation coefficient (ICC) appeared 0.99.and test–retest variability was less than 5%. These were obtained from the quantitative image assessment (SUVR). The agreement (kappa > 0.85) between test and retest scans was found on the visual read for both the qualitative (amyloid positive or amyloid negative) and semiquantitative (0 to 4) amyloid burden scores.

Special Populations

The pharmacokinetic studies in special populations were not performed. However, population analysis of PET scan data revealed no difference in florbetapir F 18 binding in AD patients or cognitively healthy controls as a function of gender, race, age or presence of medications for the treatment of AD (namenda and anticholinesterases). Also, there were no discernable differences in blood clearance kinetics between AD patients and cognitively healthy control subjects studied in trial A03.

Comparison of SUVR in different populations

Study A05 (n=184; Phase II) was conducted to show the imaging profiles in three different populations (Alzheimer Disease (AD), healthy controls (HC) and mild cognitive impairment (MCI)). The primary objective was to define a negative/positive scan and determine the rates of Aß positivity by PET imaging as a function of age in cognitively normal subjects.

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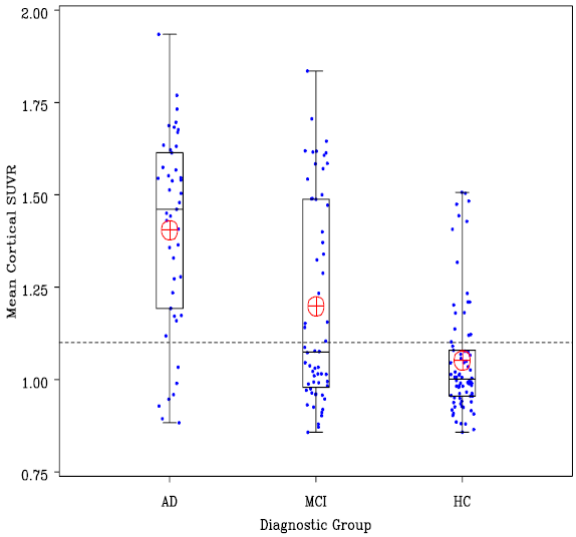

Abbreviations: AD: Alzheimer's disease; HC: cognitively normal (healthy) controls; MCI: mild cognitive impairment; SUVR: standardized uptake value ratio (region/cerebellum) Note: Individual data points are displayed with a dot and equivalent values are offset. The mean for each clinical diagnostic group is indicated by the circled plus sign, and the median is indicated by the horizontal solid line. The dotted line represents a threshold for amyloid positivity of 1.10 that was determined based on the range of young healthy controls.

The study found that in cognitively normal subjects, rates of Aβ positivity increased with age: 5.3%, 10.5%, 15.0%, and 25.0% of cognitively normal subjects aged 50 to 59, 60 to 69, 70 to 79, and 80 years or more, respectively. This confirmed that beta amyloid deposits are present in cognitively normal subjects and the amount of beta amyloid increasing with age. Thus it would be hard to rule out the presence of beta amyloids in cognitively normal aged subjects. According to the sponsor, 75.6% of subjects with AD, 38.3% of subjects with MCI, and 14.1% of cognitively normal subjects were rated as Aβ+. Subjects with clinically diagnosed probable AD were rated as negative for amyloid by qualitative rating of the 18F-AV-45 PET scan in 24.4% of cases.

The results of Study A05 show that about 20% of cognitively normal subjects would give a positive image (SUVR>1.1) on Amyvid-PET image on a visual binary read (+/-ve image). The results show that there is no correlation between a positive beta amyloid scan and cognitive function.

Correlation of SUVR with Autopsy data

One Phase III pivotal trial (Study A07) was conducted to establish correlation between florbetapir PET scan and beta amyloid pathology (autopsy cohort). The second objective of Phase III trial was to test the specificity of Florbetapir-PET scan for identifying absence of beta amyloid. The primary endpoint in autopsy cohort was to establish a correlation between the semi-quantitative visual rating (0-4) of PET scan and cortical gray matter amyloid burden at autopsy by quantitative Immunohistochemistry (IHC). The applicant has demonstrated some correlation between Florbetapir-PET images and IHC (See Figure).

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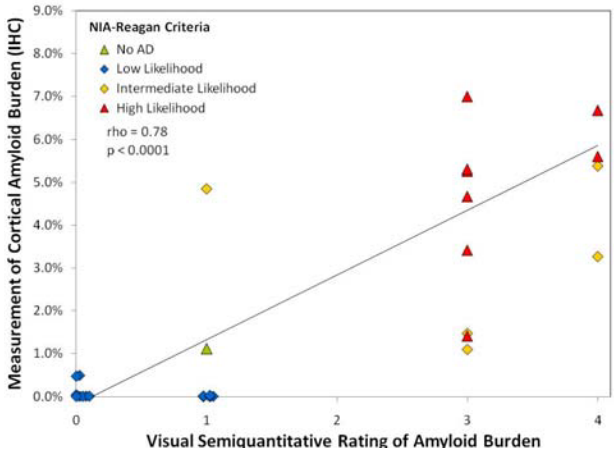
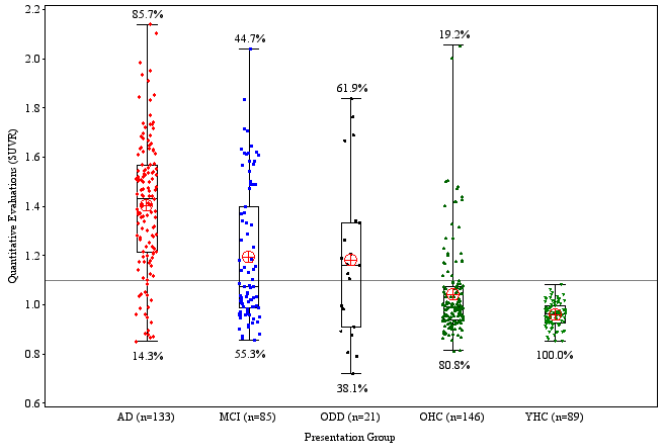


The applicant has also shown a high specificity (90-95%) in true beta amyloid negative healthy volunteers (ages 18-40). This result was expected as young healthy volunteers (18-40) do not have beta amyloid (See Figure; YHC is the young healthy control age 18-40 years old)



The applicant has not demonstrated that a true negative florbetapir-PET scan may be clinically useful in ruling out the presence of beta amyloid in the target population where the test is indicated (60 years old and above) in a blinded study.

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). Also 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 0.85 and 95% CI: 0.72 to 0.92, p<0.0001; See Figure).

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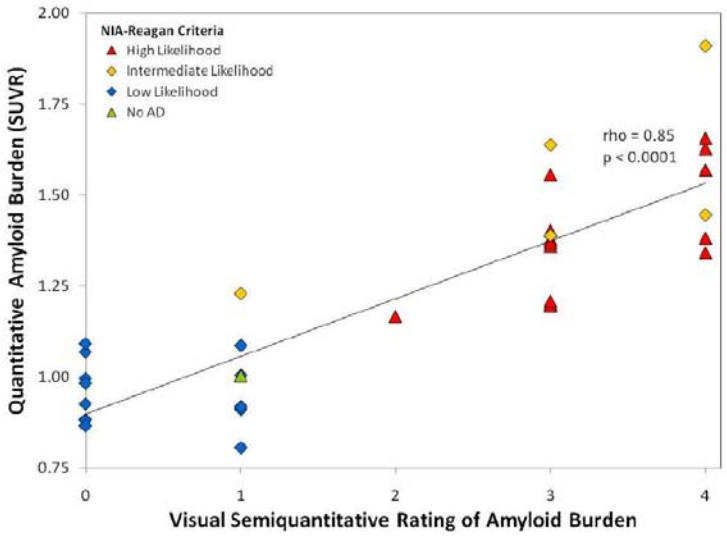

These findings suggest that the semi-automated, computerized quantitative SUVR assessment seems to be an appropriate tool for the PET image interpretation.

Conclusion

Based on the clinical pharmacology finding, the additional clinical pharmacology study is not needed, and overall the submission is acceptable.

However, the β-amyloid was found in various levels of cognitive impaired patients including healthy controls. Also the quantitative relationship between the amount of β-amyloid and level of disease is not established. Furthermore, the fundamental scientific question is remained without clear answer, i.e., whether the presence of β-amyloid is a result of certain disease, or the signal of a certain disease, e.g., AD. Therefore, one general concern remained on the proposed qualitative binary read. If the PET diagnosis appeared β-amyloid positive, the expected challengeable questions are 'How much of β-amyloid is there?' and 'How to interpret the positive scan?' In this context, an accurate, objective, and reproducible quantitative read of β-amyloid is desirable.

2. Question-Based Review:

2.1 General attributes

In clinical development, florbetapir-PET has been evaluated in two completed Phase I (A01, A02), three completed Phase II (A03, A04, A05), and one completed Phase III (A07) registration-oriented clinical trials. In addition, in study A06, an independent blinded read analysis of images acquired from subjects in studies A01 and A03 was conducted to further evaluate acceptable imaging times for florbetapir-PET post-dosing.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Florbetapir F 18 Injection is provided as a sterile solution for intravenous injection. The unit dose provided by the radiopharmacy is 370 MBq at time of calibration (time of patient injection). The formula described in Table 1 is for a unit dose of 370 MBq and a unit dose volume of 10 mL (maximum unit dose injection volume). For smaller unit dose volumes (less than 10 mL), the ratios of sodium ascorbate, dehydrated alcohol, and 0.9% Sodium Chloride Injection are maintained. The amount of each component shown in Table 1 is the maximum human dose.

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).

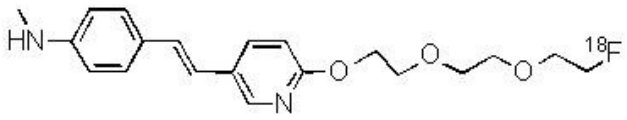

Figure 1. Chemical Structure of Amyvid

Florbetapir F-18 is a diagnostic radiopharmaceutical drug with a radioactive half life of 109.77 minutes.

The drug formulation and the roles of different ingredients are shown in Table I.

Table I. Florbetapir Composition

Component	Quality Standard	Maximum Human Dose	Function
Florbetapir F-18		370 MBq	Drug Substance
Sodium Ascorbate	USP	45 mg	(b) (4)
Dehydrated Alcohol	USP	1 mL	
0.9% Sodium Chloride Injection	USP	9 mL	

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The maximum human dose (MHD) and batch formulation for a nominal batch size of (b) (4) of Florbetapir F 18 Injection are described in Table 2. Batch volume may range from (b) (4) maintaining the same proportions of inactive components as shown in Table 2. Drug Product will be stored at controlled room temperature.

Table 2: Florbetapir F-18 injection maximum dose (MHD) and batch formula

Component	MHD	Amount per Batch[1]
Drug Substance (florbetapir F 18)	370 MBq	(b) (4)
Sodium Ascorbate, USP	45 mg	
Dehydrated Alcohol, USP	1 mL	
0.9% Sodium Chloride Injection, USP	9 mL	

[1] (b) (4)

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Florbetapir F-18 is a positron emission tomography (PET) imaging compound. The applicant is seeking the approval of this drug for PET imaging of β-amyloid aggregates in the human brain, specifically, looking for negative scan to rule out the presence of β-amyloid. This drug is the first in the class of β-amyloid PET imaging agent.

Florbetapir F 18 binds with high avidity and selectivity to β-amyloid plaques derived from 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 $K_d = 3.7 \pm 0.3$ nM. The binding of florbetapir F 18 to β-amyloid aggregates was directly visualized in brain sections from subjects with AD pathology, using autoradiographic methods. Strongly positive staining was observed in gray matter of post-mortem AD brains, but not in control tissue from subjects without AD pathology. β-Amyloid deposition was assessed using traditional neuropathological staining procedures, including Bielschowsky silver staining and immunohistochemistry with anti-Aβ antibodies. All studies demonstrated strong and statistically significant correlations between in vitro florbetapir F18 binding and β-amyloid aggregate deposition.

2.1.3 What are the proposed dosage and route of administration?

A single intravenous bolus dose of 370 MBq (10 mCi) of Amyvid is administered in a total volume not exceeding 10 mL. The minimum specific activity at the end of synthesis would be (b) (4). Taking into account the radioactive decay, at 110 minutes after synthesis, a 10 mCi (370 MBq) preparation would yield a maximum (b) (4) mass dose.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support the approval, the applicant submitted the results of one pivotal Phase 3 study, and six Phase 1 and 2 studies. Clinical pharmacology studies include PK/PD, dosimetry, biodistribution, metabolism, dose-response and test-retest reproducibility of flobetapir F-18 PET imaging. A drug-drug interaction potential was evaluated in vitro using tissue binding study.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies? Is the dose optimal?

A dose finding study (Study A03) was performed in 20 subjects (9 AD, 11 HV) with two different radioactivity doses (3 mCi and 10 mCi) to determine the amount of radioactivity needed to visualize brain uptake. 10 mCi dose provided a slightly better imaging results as compared to 3 mCi. Images were evaluated qualitatively: Images were visually examined and by semiquantitative SUVR method by a nuclear medicine specialist who was blinded to the dose in order to determine whether the 3 and 10 mCi dose levels yielded acceptable image quality for reasonable subjective differentiation between AD and healthy subjects as well as to judge the overall image quality at each dose level.

The visual assessments of the PET imaging quality for the 370 MBq (10 mCi) dose were slightly better than the 111 MBq (3 mCi) dose group. While all images were rated as "evaluable", visual assessments of the quality of the PET images revealed that 7 of 9 (80%) subjects in the 111 MBq group and 11 of 11 (100%) subjects in the 370 MBq group had quality ratings of ≥ 3 on a 5-point scale, where a score of 5 = excellent and 1 = poor. The visual differences in image quality; however, did not appear to affect the ability of the reader to identify high and low amyloid burden at the two dose levels: regional assessments of the frontal cortex, temporal cortex and precuneus revealed an assessment of high amyloid levels in 60% to 100% and 50% to 100% of AD subjects in the 111 MBq and 370 MBq dose groups, respectively, while an assessment of low to none was observed for 75% to 100% and 71% to 100% of control subjects in the 111 MBq and 370 MBq dose groups, respectively. Since the total absorbed ration dose is relatively low 7 mSv per administration for a 10 mCi dose, a dose of 10 mCi is safe and effective to visualize cortical regions of the brain.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

After intravenous administration of ^{18}F-AV-45, the total radioactivity in plasma was reduced by 80% within 10 min and by ~90% within 20 min post-injection. The total radioactivity in plasma consisted of contributions from un-metabolized parent (^{18}F -AV-

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45) and its three metabolites; ^{18}F -AV-160 (desmethyl ^{18}F -AV-45), ^{18}F -AV-267 (*N*-acetyl ^{18}F -AV-160) and ^{18}F -Polar. At 20 minutes post-injection these metabolites comprised 19%, 1% and 19%, respectively, of the circulating F-18, and the parent comprised the remaining 61% of the blood F-18 radioactivity. The metabolites have shown lower uptake in the brain and lower affinity for binding to beta amyloid thus, it is concluded that there will be minimal interference from the metabolites to the PET image from 18F-AV-45 in the brain. The excretion of radioactivity through urine accounted for 17% of the total injected activity at 200 min post-injection. The dominant species in urine was found to be 18F-Polar species (~95%) with less than 5% of parent and other metabolites.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for efficacy?

In a Phase I study the sponsor studied whether uptake and distribution of 18F-AV-45 in the brain differs between subjects with Alzheimer's disease (AD) and control. PET imaging was performed, the scans were processed to provide standard uptake value (SUV) for the following six target cortical regions (where beta amyloid plaques are found): frontal cortex, temporal cortex, precuneus, anterior cingulate, posterior cingulate, parietal cortex, and cortical average (calculated as the average of 6 regions), as well as several other brain regions including the centrum semiovale and cerebellum, which were designated as reference (background) regions. In addition, SUVRs (SUV ratios relative to cerebellum or centrum semiovale) were determined for the 6 regions.

Within 50 minutes of infusion of 18F-AV-45, subjects with AD showed accumulation of 18F-AV-45 in the frontal cortex, temporal cortex and precuneus areas (areas expected to be high in amyloid deposition), whereas healthy control subjects showed lower accumulation of tracer in these regions. At 50 minute post-injection, 18F-AV-45 had largely been cleared from the cerebellum (an area known to be free of amyloid plaques) in both AD subjects and control subjects. These differences were consistently evident in the ratio of standard uptake values (SUVR) in the target areas of the cortex relative to the cerebellum.

Thus, the cortical average SUVR 50-60 minutes post administration of 18F-AV-45 was 1.665 ± 0.175 for subjects with AD vs. 1.246 ± 0.177 for cognitively healthy controls. The time-activity (SUV) curves for cortical region and cerebellum for AD patients are given in Figure 3 and for healthy volunteers in Figure 4.

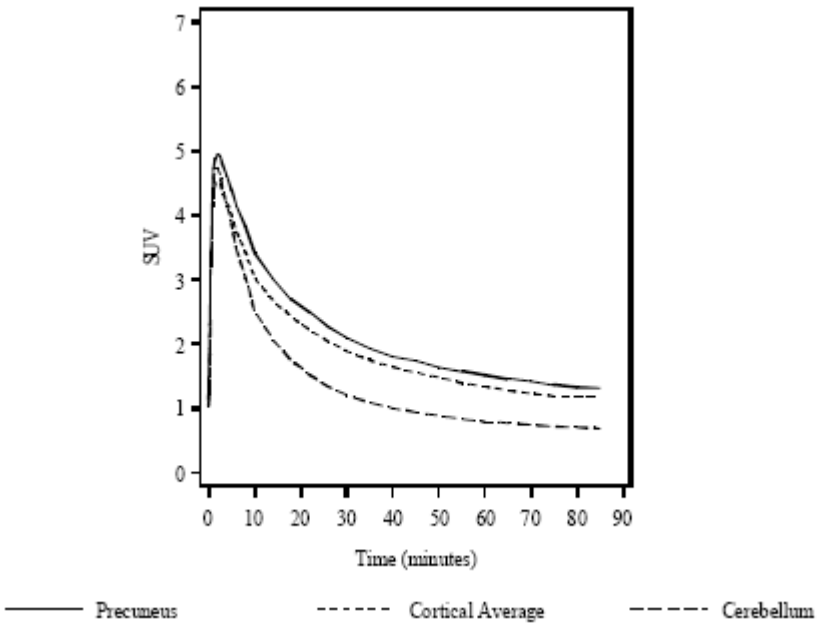

Figure 3. Mean Time Activity Curve from 0-90 min of SUV for precuneus and cortical average vs cerebellum with AD subjects

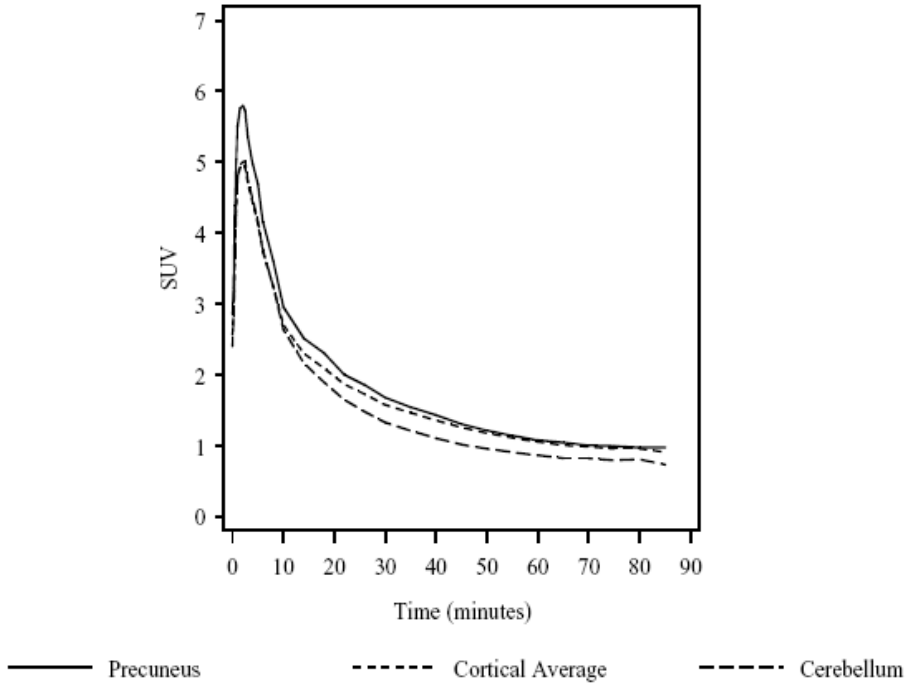

Figure 4. Mean Time Activity Curve from 0-90 min of SUV for precuneus and cortical average vs cerebellum with control subjects

2.2.4.2 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for safety?

Radiation exposure

Whole body PET imaging and biodistribution data from trial ^{18}F-AV-45-A02 were analyzed to provide organ time-integrals of F-18 radioactivity. These data were entered into OLINDA/EXM software to derive organ-specific and whole body effective radiation dosimetry results shown in Table III.

Table III. Estimated Human Radiation Dose, Amyvid (Florbetapir F 18 Injection)

	mSv/MBq		**rem/mCi**	
Organ	**Average**	**SD**	**Average**	**SD**
Adrenals	0.014	0.001	0.050	0.005
Brain	0.010	0.002	0.037	0.007
Breasts	0.006	0.001	0.023	0.003
Gallbladder Wall	0.143	0.080	0.529	0.297
Lower Large Intestine Wall	0.028	0.010	0.103	0.038
Small Intestine	0.066	0.030	0.242	0.110
Stomach Wall	0.012	0.001	0.043	0.003
Upper Large Intestine Wall	0.074	0.034	0.276	0.126
Heart Wall	0.013	0.002	0.048	0.006
Kidneys	0.014	0.001	0.048	0.004
Liver	0.064	0.022	0.238	0.082
Lungs	0.009	0.001	0.032	0.003
Muscle	0.009	0.004	0.032	0.003
Ovaries	0.018	0.004	0.065	0.016
Pancreas	0.014	0.001	0.053	0.005
Red Marrow	0.014	0.002	0.053	0.006
Osteogenic Cells	0.028	0.004	0.102	0.014
Skin	0.006	0.001	0.022	0.003
Spleen	0.009	0.001	0.033	0.004
Testes	0.007	0.001	0.025	0.005
Thymus	0.007	0.001	0.027	0.005
Thyroid	0.007	0.001	0.025	0.005
Urinary Bladder Wall	0.027	0.012	0.100	0.043
Uterus	0.016	0.003	0.058	0.012
Total Body	0.012	0.001	0.043	0.004
Effective Dose	0.019	0.004	0.069	0.016

The organs with the highest radiation exposure are the gallbladder wall, small intestines, upper large intestine wall, and liver. The human effective dose is approximately 0.019 mSv/MBq or 7 mSv (0.7 rem) for a 370 MBq (10 mCi) dose.

2.2.4.3 Does this drug prolong the QT or QTc interval?

The subjects were monitored by EKG after i.v. administration of florbetapir. No consistent and clinically significant changes in vital signs or ECG were observed at any point during the study. There was an increase of 6.0 (± 9.79) mmHg in systolic blood pressure in the control group from baseline to the 90 minutes time point, but there was no significant increase in this group at either 0 minutes post dose or at the end of study assessment, and there were no significant changes in systolic blood pressure in the AD group at any time point. No subjects experienced increases of more than 60 msec from baseline in QTc as calculated by either the Bazett or the Fridericia formulae at any time point during the study. No QTc values exceeded 500 msec at any time point during the study. The mean increase from baseline did not exceed 10 msec at any time point. No statistically or clinically significant changes in QTc were noted at the time of peak plasma concentration (immediately after injection) or at study end. However, a small, but statistically significant increase in QTc (4.2 msec by Bazett and 5.8 msec by Fridericia formulae), was noted 90 minutes post-administration.

2.2.4.4 Is the dose and imaging time window selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

To test whether a qualitative read of a Florbetapir-PET scan collected at 30-40 minutes post-injection (the 30 minute image) provides equivalent results to the qualitative read of a scan collected at 50-60 minutes post-injection (the 50 minute image), the sponsor conducted a clinical study. The objectives of the study were to:

To compare the results a semi-quantitative read of the 30 minute image to a semi-quantitative read of the 50 minute image. • To measure and summarize inter-reader reliability for qualitative and semi-quantitative assessments of the 30 minute image and the 50 minute image. • To measure and summarize SUVRs obtained from images at 30 minutes and 50 minutes.

Three (3) independent readers (i.e. not involved in subject enrollment) who were blinded to subject identification, subject diagnosis, subject demographics and PET scan time points post-injection, randomly and independently read florbetapir-PET scans and scored the images per the Independent Review Charter. The readers completing the qualitative and semi-quantitative evaluations for this analysis had participated as readers on prior Avid Radiopharmaceutical studies. The readers received training for this evaluation, which included a comprehensive review of florbetapir-PET images from previous studies along with an Avid Radiopharmaceutical reader manual to aid and serve as a reference for the reader during live reading sessions.

On imaging day, subjects were administered with either 3mCi (5 AD and 4 HV in study A03) or 10mCi of florbetapir F 18 (3 AD and 7 HV from study A03 and 10 AD and 12 HV in Study A01) after which brain PET imaging commenced continuously for up to 90 minutes.

Brain PET scans are categorized as either Aß+ or Aß- by visual reads and evaluations of three readers who were blinded to subject identification, subject diagnosis, subject demographics and PET scan time points post-injection. Qualitative scores are summarized by the majority score of the 3 readers. The majority score is used for analysis purposes. The agreement between the two time points was reported and summarized using agreement statistics. Using the 50 minute post-injection majority score of the 3 readers as the reference, the hypothesis tested was that the 30 minute majority score of the 3 readers will have an observed agreement with the reference of at least 0.85. Agreement between the two time points was computed using a kappa statistic.

Brain PET scans were scored using a 5-point scale between 0 and 4 based on observed severity of amyloid presence by visual reads and evaluations of three readers who were blinded to subject identification, subject diagnosis, subject demographics and PET scan time points post-injection. Semi-quantitative scores were summarized by the median score of the 3 readers. The median score was used for analysis purposes. Statistics were presented for the overall population and by diagnostic subgroup. The semi-quantitative assessments are summarized using counts and agreement between the 30 minute post-injection score and the 50 minute post-injection score. Equivalence between the two time points was examined using a quadratic weighted kappa statistic. In addition, the correlation between 30 minute post-injection scores and 50 minute post-injection scores were calculated and a scatter plot is provided (Figure 5).

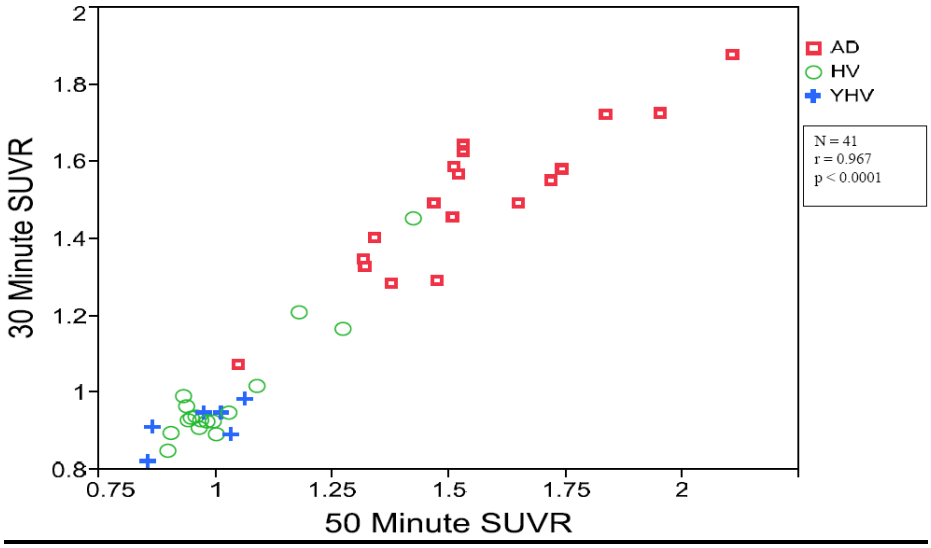

Figure 5. PET imaging time window correlation for 30 min and 60 min SUVR

A sample amyvid PET image and scoring system in shown is Figure 6.

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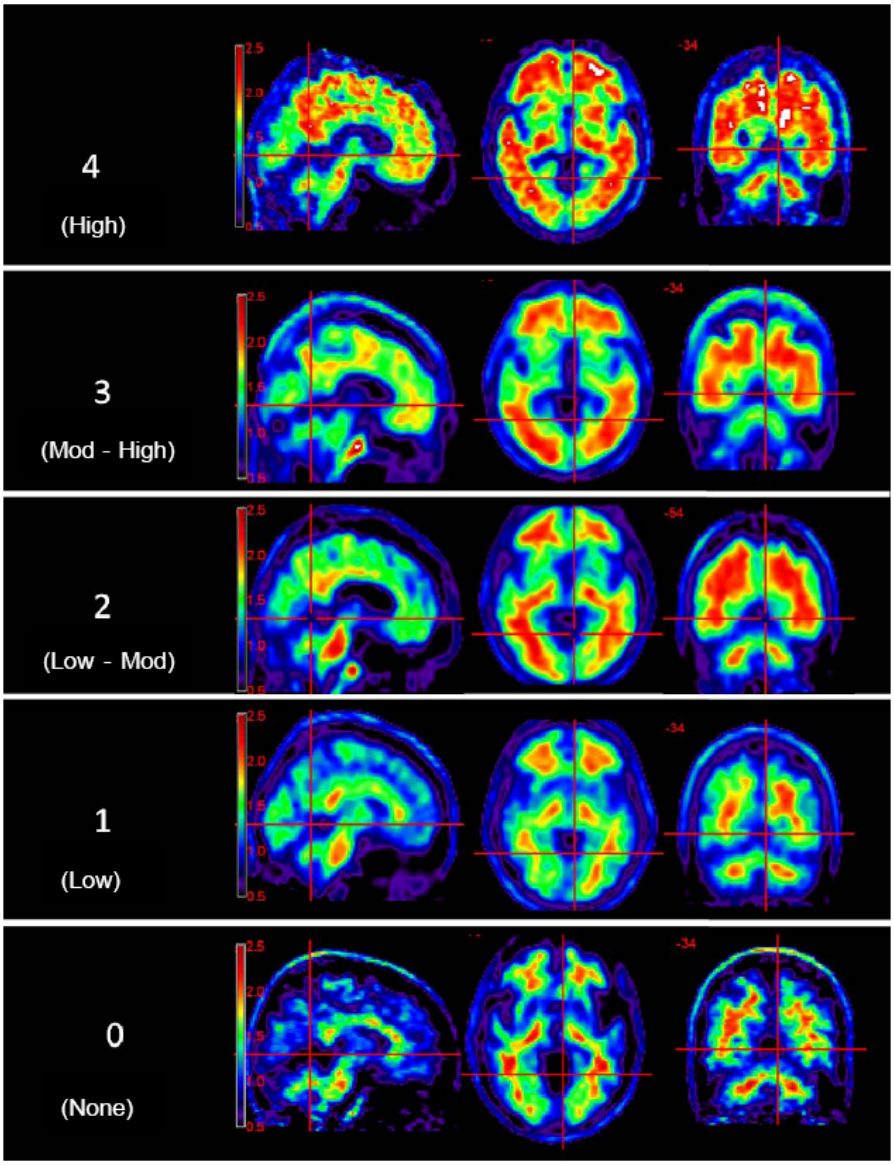

Figure 6. Sample PET Images with Reader Scores

Has the sponsor demonstrated the reproducibility of the results in AD patients and in healthy volunteers? Or Has the sponsor demonstrated the agreement between test/retest of the PET imaging with Amyvid?

A clinical study (A04) was conducted at 4 study centers. The objective of the study was to evaluate test-retest reproducibility of 18F-AV-45 for brain imaging of amyloid in healthy volunteers and subjects with Alzheimer's disease (AD). A total of 25 subjects were enrolled: 21 subjects (11 subjects with AD and 10 healthy volunteers) were enrolled in the primary test-retest phase of the study. Each subject was imaged on 2 separate days not more than 4 weeks apart.

Both the SUVs and SUVRs were highly reproducible between test and retest image results for AD and control subjects whether comparing the 10-minute (50 to 60 minutes post-injection) or 20-minute (50 to 70 minutes post-injection) scans. SUVRs for the cortical average relative to cerebellum of test vs. retest 20-minute scans were 1.42 ± 0.25 vs. 1.41 ± 0.27 for AD subjects and 1.00 ± 0.06 vs. 1.01 ± 0.06 for control subjects. The same reproducible trend was observed when the centrum semiovale was used as the reference instead of the cerebellum.

The intrasubject test/retest variability was assessed using the SUVR (relative to cerebellum and relative to centrum semiovale) from the retest imaging scan result relative to the test imaging scan result. The intrasubject test/retest variability for the 10- and 20-minute scans for SUVRs of target cortical region relative to cerebellum are summarized in Table IV. Intrasubject test-retest variability for cortical average SUVR (cerebellum) over the 50 to 70-minute time period was 2.4% for AD subjects and 1.5% for controls. Across cortical target regions, intrasubject variability ranged from 2.3% to 3.3% in AD subjects and from 1.4% to 2.9% in controls.

Table IV. Test-Retest Variability of Amyvid in AD Patients and Healthy Controls

	AD Subjects	Control Subjects
Brain Region	% Difference 50 to 70 minutes N=10	% Difference 50 to 70 minutes N=9 [a]
Cortical average	2.35 ± 1.413	1.49 ± 0.839
Frontal cortex	3.26 ± 2.196	1.38 ± 1.281
Temporal cortex	2.34 ± 1.408	2.85 ± 1.656
Precuneus	2.98 ± 2.088	2.23 ± 2.545
Average frontal cortex, temporal cortex, and precuneus	2.65 ± 1.225	1.59 ± 1.464
Posterior cingulate	2.61 ± 1.791	2.81 ± 1.813
Anterior cingulate	2.35 ± 1.452	2.89 ± 2.769
Parietal cortex	3.32 ± 1.894	2.87 ± 2.595

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

The metabolism and clearance of florbetapir F 18 in humans were evaluated in Studies A01 and A03. Florbetapir F 18 is very rapidly cleared (Figure 7) from circulation post-intravenous injection. In the principal PK/metabolism study, A03, it was determined that less than 5% of the injected F-18 radioactivity remains in blood by 20 minutes following administration. The residual activity in circulation at that time included low levels of parent florbetapir F 18 (1.2% of initial dose), the desmethyl derivative (AV-160 at 1% of initial dose), and polar metabolites (1.5% of initial dose). By 90 minutes, less than 2% of

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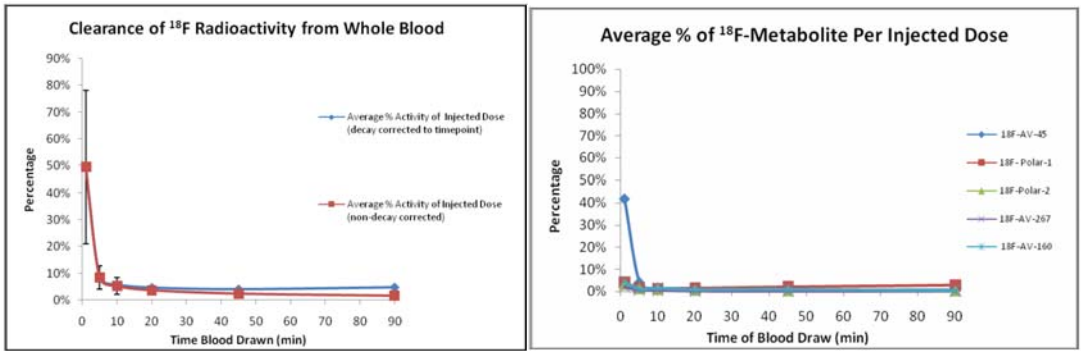
the injected F-18 remained in circulation and essentially all of the F-18 in circulation at that time was in the form of more polar metabolites of florbetapir F 18.

Figure 7. Clearance of Florbetapir F-18 and metabolite from whole blood



Study A02 evaluated the whole body distribution and elimination by means of serial whole body imaging. Rapid brain penetration and washout was observed in normal subjects along with rapid blood clearance. Consistent with other study results suggesting hepatic metabolism, the whole body scans demonstrated rapid accumulation of F-18 in the liver, followed by biliary excretion into the GI tract.

^{18}F-AV-45 undergoes significant metabolism after intravenous injection (Figure 8). Total radioactivity in plasma was reduced by 80% within 10 min and by ~90% within 20 min post-injection. The total radioactivity in plasma consisted of contributions from un-metabolized parent (^{18}F -AV-45) and its three metabolites; ^{18}F -AV-160 (desmethyl ^{18}F -AV-45), ^{18}F -AV-267 (*N*-acetyl ^{18}F -AV-160) and ^{18}F –Polar (Figure 9). At 20 minutes post-injection these metabolites comprised 19%, 1% and 19%, respectively, of the circulating F-18, and the parent comprised the remaining 61% of the blood F-18 radioactivity. The metabolites have shown lower uptake in the brain and lower affinity for binding to beta amyloid thus, it is concluded that there will be minimal interference from the metabolites to the PET image from ^{18}F-AV-45 in the brain. The excretion of radioactivity through urine accounted for 17% of the total injected activity at 200 min post-injection. The dominant species in urine was found to be 18F-Polar species (~95%) with less than 5% of parent and other metabolites.

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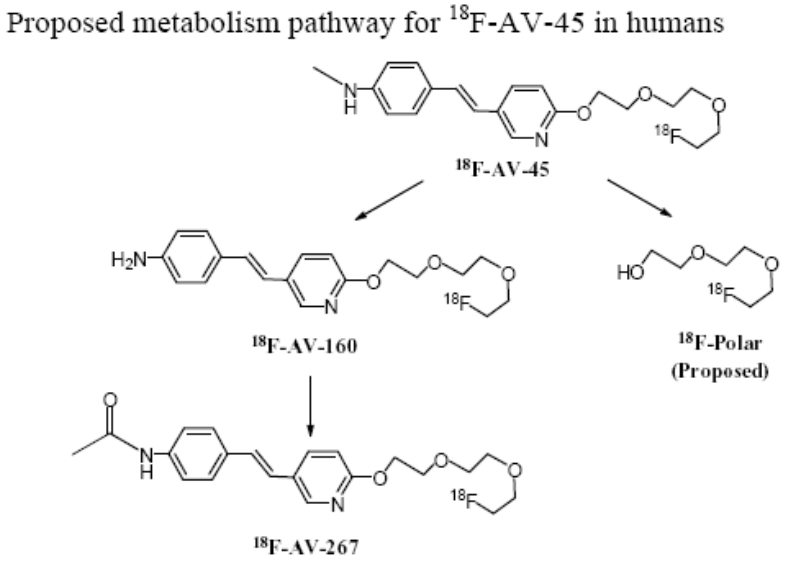

Figure 8. Metabolic Pathway for Florbetapir

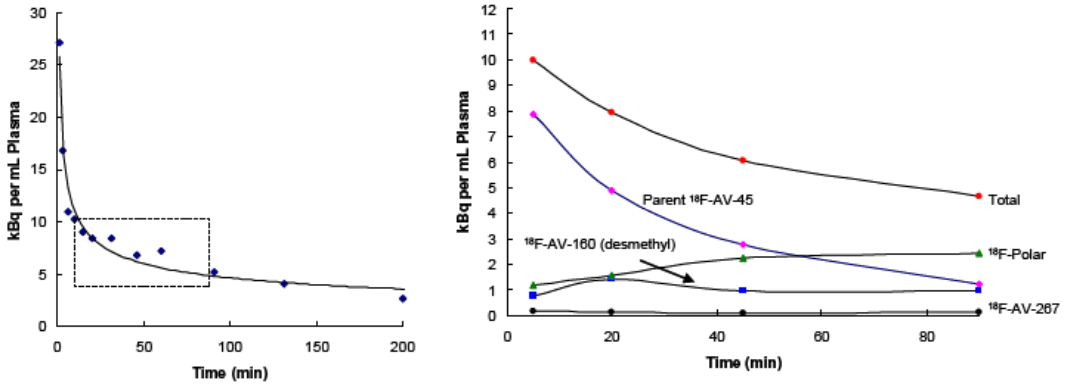

Figure 9. Clearance of radioactivity from plasma over time (n=2). The component of total radioactivity and the rate of metabolism of 18F-AV-45 and rates of formation of various metabolites

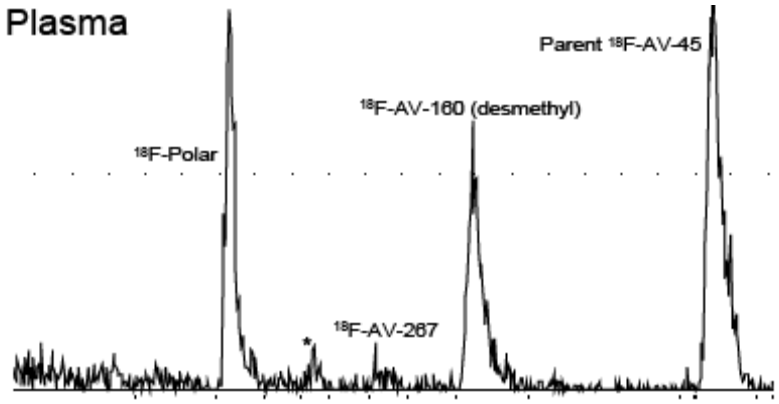

Figure 10. High-pressure liquid chromatographic separation profile with radiometric detection of plasma sample 20 min after an injection of 18F-AV-45. The peak marked with an asterisk is an impurity present in the dose of 18F-AV-45. 18F-polar species represent ~19%, 18F-AV-160 represents ~19%, the N-acetyl metabolite 18F-AV-267 represents 1% and parent 18F-AV-45 represents ~61% of the blood radioactivity at this time point.

The radiometric HPLC analysis of the metabolite in urine sample is given in Figure 10 and Figure 11. The HPLC trace shows F-18 labeled polar component as the major metabolite.

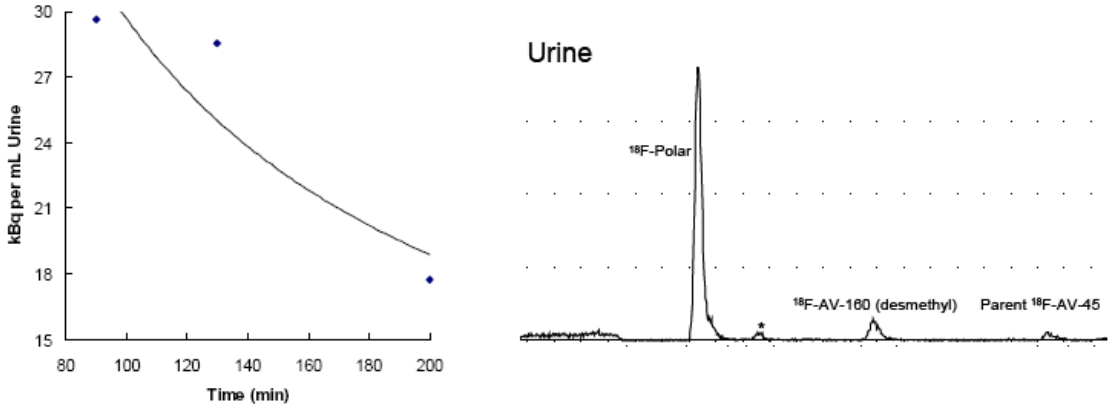

Figure 11. Left: Clearance of radioactivity through urine over time (right). Right: High-pressure liquid chromatographic separation profile with radiometric detection of urine sample 75 min after an injection of 18F-AV-45. The peak marked with an asterisk is an impurity present in the dose of 18F-AV-45.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
See 2.2.5.1**.**

2.2.5.3 What are the characteristics of drug absorption?
Not applicable as flobetapir is to be used as single intravenous injection.

2.2.5.4 What are the characteristics of drug distribution?
See 2.2.5.1.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?
See 2.2.5.1.
Study A02 evaluated the whole body distribution and elimination by means of serial whole body imaging. Rapid brain penetration and washout was observed in normal subjects along with rapid blood clearance. Consistent with other study results suggesting hepatic metabolism, the whole body scans demonstrated rapid accumulation of F-18 in the liver, followed by biliary excretion into the GI tract.

2.2.5.6 What are the characteristics of drug metabolism?
See 2.2.5.1.

2.2.5.7 What are the characteristics of drug excretion?
See 2.2.5.1.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?
Not assessed.

2.2.5.9 How do the PK parameters change with time following chronic dosing?
Not applicable as flobetapir is to be used as single use.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?
NA

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?
The pharmacokinetic studies in special populations were not performed. However, population analysis of PET scan data revealed no difference in florbetapir F 18 binding in

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AD patients or cognitively healthy controls as a function of gender, race, age or presence of medications for the treatment of AD (namenda and anticholinesterases). Also, there were no discernable differences in blood clearance kinetics between AD patients and cognitively healthy control subjects studied in trial A03.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients
Amyvid PET imaging is not to be performed in pediatric subjects. A pediatric waiver has been granted.

2.3.2.2 Renal impairment
NA

2.3.2.3 Hepatic impairment
There are no adequate and well-controlled studies in patients with hepatic impairment using flobetapir.

2.3.2.4 What pregnancy and lactation use information is there in the application?
There are no adequate and well-controlled studies in pregnant women using flobetapir and no data on the use of flobetapir in nursing mothers.

2.4 Extrinsic Factors

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?
The pharmacokinetic studies in special populations were not performed. However, population analysis of PET scan data revealed no difference in florbetapir F 18 binding in AD patients or cognitively healthy controls as a function of gender, race, age or presence of medications for the treatment of AD (namenda and anticholinesterases). Also, there were no discernable differences in blood clearance kinetics between AD patients and cognitively healthy control subjects studied in trial A03.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?
Four medications are currently approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) to treat the cognitive manifestations of AD: three are acetylcholinesterase inhibitors and memantine, an

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NMDA receptor antagonist. Given the ubiquitous drug use in the elderly and AD population, the possibility of drug drug
interactions at the ^{18}F-AV-45 binding site needs to be evaluated. To determine the possible effects of commonly used drugs and drug candidates on ^{18}F-AV-45 binding to β -amyloid, an in vitro tissue binding assay and in vitro film autoradiography were performed by the sponsor.

A total of 23 drugs were studied to determine the effects on binding of 18F-AV-45. The study showed that none of the drugs interfered with 18F-AV-45 binding to β-amyloid at therapeutically meaningful concentrations. The drugs tested included the following approved drugs: NSAIDs ibuprofen, naproxen, and celecoxib; the acetylcholinesterase inhibitors tacrine, physostigmine, galantamine and donepezil; the cholesterol-lowering drug simvastatin; the anti-diabetic drug troglitazone; the anti-psychotic drug haloperidol; the anxiolytic diazepam; and the antidepressants citalopram, fluoxetine, paroxetine, and nisoxetine. In addition, one anti-Aβ-antibody currently in clinical studies and four γ-secretase inhibitors (L-685458, S1288, Compound W, and DAPT) were tested. The findings did not identify any risk for drug-drug interactions at the 18F-AV-45 binding site.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?
NA

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?
NA

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
NA

2.4.2.5 Are there other metabolic/transporter pathways that may be important?
NA

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?
NA

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are coadministered?
No formal drug-drug interaction studies were conducted with flobetapir.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?
Not applicable as the formulation is for IV administration.

2.5.2 What is the composition of the to-be-marketed formulation?
The drug formulation and the roles of different ingredients are shown in Table I.

Table I. Florbetapir Composition

Component	Quality Standard	Maximum Human Dose	Function
Florbetapir F-18		370 MBq	Drug Substance
Sodium Ascorbate	USP	45 mg	(b) (4)
Dehydrated Alcohol	USP	1 mL	
0.9% Sodium Chloride Injection	USP	9 mL	

2.5.3 What moieties should be assessed in bioequivalence studies?
Not applicable.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?
Not applicable.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?
Not applicable.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?
Yes.

2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?
Yes.
Clearance of 18F-AV-45 from plasma was determined by collecting 1 mL of whole blood

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at various time-points following injection of 10 mCi of 18F-AV-45; plasma was separated from other blood components by centrifugation for 10 min at 5000 rpm on a Beckman centrifuge. The plasma fraction from each time-point was eluted through a plasma separator tube. A 0.2 mL portion of the plasma fraction was counted in a gamma counter for total activity and plotted versus time after correction for decay between collection and counting of samples. Similarly, a 0.2 mL portion of urine sample was counted in a gamma counter for total activity and plotted versus time after correction for decay between collection and counting of samples.

For metabolism, the plasma separated from other blood components was mixed with 6 g of urea to dissociate protein bound compounds. The entire mixture was injected onto a high-pressure liquid chromatography system. The HPLC system consisted of an isocratic pump with a dual column switch connected to an Eclipse XDB-C18 reversed-phase column and to a size exclusion column. Protein and other extraneous components were separated by a dual column switch system. Briefly, after loading the plasma sample on to the HPLC loop, the sample was transferred to a size-exclusion column and washed with 10% acetonitrile-water solvent for 4 min. After this time, the materials retained on the size-exclusion column were transferred to the C18 reversed-phase column and eluted with a solvent containing 55% acetonitrile and 45% 20 mM ammonium acetate in water. The flow rate was 1 mL/min for 10 min followed by 2 mL/min. All of the radiometric species were detected using a Bioscan radiometric in-flow detector. The radiometric chromatogram was integrated for area under the peaks (with a correction factor for the flow rate) to a total area of 100%. All the peaks present in 18F-AV-45 for Injection (reference) were not integrated in the chromatograms from plasma samples. Each of the peaks in the chromatogram was identified by using reference compounds eluted under identical HPLC conditions.

3. DETAILED LABELING RECOMMENDATIONS

On relevant clinical pharmacology sections are included.

The sponsor's proposal	FDA recommendations
Black	Strike through for deletion. Italic and Underlined for addition Comment: Bold

Tabel of content: 12.4 is designated number for pharmacogenomics. The dosimetry data should be move to under the section of dosage and administration.

7. DRUG INTERACTIONS

(b) (4)

[redacted]

12. CLINICAL AND NONCLINICAL PHARMACOLOGY

12.1. Mechanism of Action

(b) (4)

[redacted]

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5 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

4 APPENDICES

4.1. Proposed Package Insert (Original and Annotated)

Not attached

4.2. Individual study reviews

4.2.1 Study A01

4.2.2 Study A02

4.2.3 Study A03

4.2.4 Study A04

4.2.5 Study A05

4.2.6 Study A06

4.2.7 Study A07

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1. Title Page

A preliminary evaluation of the amyloid binding properties, pharmacokinetics and safety of ^{18}F-AV-45 in healthy elderly volunteers and patients with Alzheimer's disease

Protocol Number:	^{18}F-AV-45-A01
Phase:	1
Study Drug:	^{18}F-AV-45
Indication Studied:	Alzheimer's disease
Study Design:	Open-label, multicenter study evaluating the brain uptake and distribution, as well as the pharmacokinetics, metabolism, and safety of ^{18}F-AV-45 in 16 healthy elderly subjects and 16 subjects with Alzheimer's disease.
First Subject Enrolled:	19 June 2007
Last Subject Completed:	14 January 2008
Sponsor:	Avid Radiopharmaceuticals, Inc
	Sponsor's Responsible Medical Officer: Daniel M. Skovronsky, MD, PhD
	Sponsor's Contact Person: Michael J. Pontecorvo, PhD Telephone: 215-966-6221 Fax: 413-826-0416
Report Date	12 October 2009

This study was performed in compliance with the principles of good clinical practice (GCP). The information contained in this Clinical Study Report is CONFIDENTIAL and the information contained within it may not be reproduced or otherwise disseminated without the approval of Avid Radiopharmaceuticals.

Flobetapir NDA 202-008
Reference ID: 2904801

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals, Inc.	^{18}F-AV-45 for Injection	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

Title of Study: ^{18}F-AV-45-A01

A preliminary evaluation of the amyloid binding properties, pharmacokinetics and safety of ^{18}F-AV-45 in healthy elderly volunteers and patients with Alzheimer's disease

Test Product: ^{18}F-AV-45

Dose: 10 mCi (370 MBq)

Route of Administration: Intravenous (IV) bolus

Study Phase: I

Study Centers: The study was conducted at 3 study centers: The Johns Hopkins University (site 012, Dr. Wong), The Memory Enhancement Center (site 023, Dr. Ross), and Community Health Research (site 126, Dr. Edell). A fourth center, Wake Forest University was IRB approved, but no subjects were screened or enrolled at this center.

Objectives:

The primary objective of this protocol was to address the feasibility for further development of ^{18}F-AV-45 as an amyloid targeted radiopharmaceutical. Specifically, the trial evaluated ^{18}F-AV-45 in order to:

- Determine whether uptake and distribution of ^{18}F-AV-45 in the brain differs between subjects with Alzheimer's disease (AD) and controls;
- Obtain a preliminary evaluation of the pharmacokinetics (PK) of ^{18}F-AV-45 in healthy volunteers and subjects with AD;
- Obtain preliminary information regarding the safety of ^{18}F-AV-45 in healthy volunteers and subjects with AD; and
- Obtain preliminary information regarding dosimetry of ^{18}F-AV-45 in healthy volunteers.

Number of Subjects (Enrolled):

Sixteen (16) healthy volunteers and 16 subjects with AD were enrolled. Three (3) of the healthy volunteers were to have whole body scans to obtain biodistribution information to calculate preliminary dosimetry measurements. Imaging technical difficulties precluded attenuation correction and reconstruction in the first subject, so a whole body scan was conducted on an additional subject (total = 4) to provide usable biodistribution data for three subjects.

Eligibility:

Subjects with AD were enrolled if they:

- Were males or females greater than 50 years of age;
- Met the National Institute of Neurological and Communication Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD

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and had a Mini Mental State Examination (MMSE) score at screening between 10 and 24 inclusive;

- Had a caregiver who could report on their mental status and activities of daily living; and
- Gave informed consent. If the subject was incapable of informed consent, the caregiver could consent on behalf of the subject (the subject still confirmed assent).

Healthy volunteers were enrolled if they:

- Were males or females greater than 50 years of age;
- Had a MMSE score $\geq$ 29, and were cognitively normal on the psychometric test battery at screening; and
- Gave informed consent.

Subjects were excluded from enrollment if they:

- Had a history of, or a current clinically significant neurologic disease (other than AD, as appropriate);
- Had evidence from magnetic resonance imaging (MRI) or other biomarker studies that suggested an etiology of dementia other than AD, or in the case of cognitively normal volunteers, had evidence from MRI or other biomarkers indicating presence of AD pathology;
- Had current clinically significant cardiovascular disease or clinically significant abnormalities on screening electrocardiogram (ECG) (including but not limited to QTc>450 msec);
- Had current clinically significant psychiatric disease. Subjects with behavioral dysfunction in AD could be entered only after discussion and with the approval of the sponsor;
- Had a current clinically significant endocrine or metabolic disease, pulmonary, renal or hepatic impairment, or cancer;
- Had clinically significant infectious disease, including AIDS or HIV infection or previous positive test for hepatitis B, hepatitis C, HIV-1, or HIV-2;
- Had a history of alcohol or substance abuse or dependence;
- Were women of childbearing potential not refraining from sexual activity or not using adequate contraception;
- Required medications with a narrow therapeutic window (eg, warfarin), were receiving any investigational medications, or had participated in a trial with investigational medications within the last 30 days. Treatment with psychotropic medication was not forbidden, but investigators were instructed to carefully consider whether subjects requiring psychotropic medications would be able to complete the imaging session; or
- Had ever participated in an experimental study with an amyloid targeting agent (eg, immunotherapy, secretase inhibitor) unless it could be demonstrated that the subject received only placebo in the course of the trial. Subjects with AD could be on a stable dose of an anticholinesterase and/or Namenda, and could be taking Vitamin E at the time of imaging. Other approved or over-the-counter (OTC) treatments for dementia (eg, Ginkgo) were prohibited.

Study Design:

This study assessed the brain uptake and distribution, as well as the PK, metabolism, and safety of ^{18}F-AV-45 in 16 healthy volunteers and 16 subjects with AD. In all subjects, screening assessments included demographic information, cognitive testing, safety assessment and an MRI scan. Subjects who qualified for the study returned to the clinic at a later date and had catheters placed for IV drug administration and for blood sampling. Vital signs, ECG and blood samples were obtained. All subjects then received a single IV bolus of approximately 10 mCi (370 MBq) ^{18}F-AV-45 and positron emission tomography (PET) imaging began. Four (4) healthy volunteers had whole body scans to obtain biodistribution information

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and to calculate preliminary dosimetry measurements (Group A). Subjects in this group had brain imaging for 20 minutes, total body imaging for 15-25 minutes, and brain imaging again for 40-55 minutes (90 minutes total). The subjects were allowed to rest outside of the scanner for 20 minutes. Brain imaging resumed at 120 minutes for another 20 minutes, followed by another rest period. Total body imaging resumed for 15-25 minutes, followed by brain imaging for 20 minutes. Subjects ended the study at approximately 200 minutes. The remaining subjects (Group B) had brain imaging continuously for a period of 90 minutes. The subjects were then allowed to rest outside the scanner for approximately 30 minutes. Brain imaging resumed at 120 minutes for another 20 minutes, followed by another rest period. The subjects were then allowed to rest outside the scanner for approximately 40 minutes. Brain imaging resumed at 180 minutes for a final 20 minutes. The protocol anticipated that the scanning procedure might be shortened if the later time points were not yielding critical information, and in accordance with the protocol, the 120 and 180 minute scans were eliminated after the first 3 subjects. In 5 subjects, arterial (012-004 and 012-005) or venous (012-001, 012-019, and 012-020) blood samples and urine samples were taken at multiple time points in order to better understand the PK and metabolism of ^{18}F-AV-45. ECG and vital signs were obtained prior to injection, immediately post-administration of ^{18}F-AV-45 (0 minute time point), 90 minutes post-administration, and at the end of the study (approximately 200 minutes after administration of ^{18}F-AV-45). Adverse events and serious adverse events were collected continuously throughout the course of the study. A physician saw the subject at screening, prior to administration of ^{18}F-AV-45, and prior to discharge. Subjects who experienced an adverse event were not discharged until the event had resolved or stabilized.

Assessments and Endpoints:

Screening: Day 0

Screening assessments for all subjects included:

- Informed consent;
- Demographics (age, sex, education, alcohol and drug use, smoking);
- Medical history, physical and neurological exam, concomitant medications;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of neurologic disease);
- Cognitive testing (MMSE, Alzheimer's Disease Assessment Scale (ADAS), psychometric battery);
- Safety (vital signs, ECG, clinical labs); and
- MRI (If an MRI had been performed within the last six months and results were available for possible use in normalizing regions of interest from the PET scan, the MRI was not repeated).

Imaging: Day 1

The following assessments were performed for Group A subjects (4 healthy volunteers):

- Brain imaging for 20 minutes, total body imaging for 15-25 minutes, and brain imaging again for 40-55 minutes (90 minutes total). The subjects were allowed to rest outside of the scanner for 20 minutes. Brain imaging resumed at 120 minutes for another 20 minutes, followed by another rest period. Total body imaging resumed for 15-25 minutes, followed by brain imaging for 20 minutes. Subjects ended the study at approximately 200 minutes;
- Vital signs were taken immediately prior to administration of ^{18}F-AV-45, immediately and 90 minutes after ^{18}F-AV-45 administration, and at the end of the study (after completion of PET scanning, approximately 200 minutes after administration of ^{18}F-AV-45);

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- ECGs were taken two times (5 minutes apart) immediately prior to ^{18}F-AV-45 administration, immediately and 90 minutes after ^{18}F-AV-45 administration, and after completion of PET scanning and collection of vital signs, at the end of the study;
- In 3 Group A subjects (012-001, 012-004 and 012-019), blood samples for metabolite analysis were taken at multiple time points;
- Blood and urine samples were collected for clinical labs prior to administration of ^{18}F-AV-45 and at the end of the study;
- Subjects were observed continuously for signs of adverse events or serious adverse events; and
- A physician saw the subject prior to discharge.

The following assessments were performed for Group B subjects (12 healthy volunteers, 16 AD subjects):

- Brain imaging continuously for a period of 90 minutes. The subjects were then allowed to rest outside the scanner for approximately 30 minutes. Brain imaging resumed at 120 minutes for another 20 minutes, followed by another rest period. The subjects were then allowed to rest outside the scanner for approximately 40 minutes. Brain imaging resumed at 180 minutes for a final 20 minutes. The protocol anticipated that the scanning procedure might be shortened if the later time points were not yielding critical information, and in accordance with the protocol, the 120 and 180 minute scans were eliminated after the first 3 subjects;
- Vital signs were taken immediately prior to administration of ^{18}F-AV-45, immediately and 90 minutes after ^{18}F-AV-45 administration, and at the end of the study (after completion of PET scanning, approximately 205 minutes after administration of ^{18}F-AV-45);
- ECGs were taken two times (5 minutes apart) immediately prior to ^{18}F-AV-45 administration, immediately and 90 minutes after ^{18}F-AV-45 administration, and after completion of PET scanning and collection of vital signs, at the end of the study;
- In 2 subjects (012-005 and 012-020), blood samples for metabolite analysis were taken at multiple time points;
- Blood and urine samples were collected for clinical labs prior to administration of ^{18}F-AV-45 and at the end of the study;
- Subjects were observed continuously for signs of adverse events or serious adverse events; and
- A physician saw the subject prior to discharge.

Evaluation of Imaging:

PET images for each subject were re-sliced (realigned) to create a mean image across all of the frames (individual acquisition time blocks). This image was normalized to Talairach space by statistical parametric mapping (SPM), version 2. Each individual frame was then fitted to this normalized mean image. Template volumes of interest (VOI) were created for frontal, temporal, parietal, occipital, anterior cingulate, posterior cingulate and precuneus cortical grey matter. Cerebellar grey matter and centrum semiovale white matter were used as reference regions. The template VOI were overlaid on the individual scans and counts were extracted from each region. Standard uptake values (SUV), SUV time-activity curves, and SUV ratios (SUVRs) to reference regions were then generated from the VOI for each frame.

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Statistical Methods:

Demographic variables and cognitive scales were summarized using descriptive statistics for each group (AD and control). Safety variables included biodistribution data, adverse event count, laboratory parameters, vital signs, and ECG. Comparisons were generally made to baseline, as appropriate. Descriptive statistics were used to help detect changes within groups or differences between groups. Adverse events were summarized in terms of number and percentage of subjects experiencing an adverse event. For purposes of summarizing adverse events, only adverse events spontaneously reported to have occurred within 3 days of administration of ^{18}F-AV-45 were reported. Any serious adverse events spontaneously reported to have occurred within 30 days of the dose of ^{18}F-AV-45 were reported.

This report includes estimates of SUVs for 7 cortical target VOIs: frontal cortex, temporal cortex, parietal cortex, occipital cortex, anterior cingulate, posterior cingulate, and precuneus as well as the cortical average (calculated as the average of the prior 7 regions). In addition, the ratios of these SUVs (SUVRs) relative to the cerebellum and relative to the centrum semiovale were calculated. These data were summarized for subjects with AD and healthy elderly controls for each imaging time point and for the 30- to 90-minute period in 5-minute, 10-minute and 15-minute blocks for further analysis of time-activity trends. Means, standard deviations, medians, and minimum and maximum values are presented for each variable calculated.

Results:

Subjects/Disposition

Sixteen (16) cognitively normal healthy volunteers and 16 AD subjects qualified for the study and received ^{18}F-AV-45 followed by PET imaging. The mean MMSE was 29.8 for the volunteers and 19.3 for the AD subjects. All subjects were included in the safety analysis. Imaging data for 1 cognitively normal healthy volunteer and 5 AD subjects were excluded from the efficacy analysis due to technical difficulties. Thus, valid imaging data for a total of 15 controls and 11 AD subjects were included in the efficacy analysis.

Safety Results

No serious adverse events occurred. Two subjects experienced treatment-emergent adverse events. Subject 023-001 reported a mild headache that the investigator considered possibly related to the investigational compound. Subject 026-001 experienced moderate claustrophobia while in the scanner, which the investigator considered remotely (unlikely) related to the investigational compound. Neither adverse event resulted in discontinuation of the study. One subject with AD, subject 023-006, withdrew consent approximately 5 minutes after injection of study drug, at start of the PET scanning, but this was not recorded as an adverse event by the investigator.

No consistent and clinically significant changes in vital signs or ECG were observed at any point during the study. There was an increase of 6.0 (± 9.79) mmHg in systolic blood pressure in the control group from baseline to the 90 minutes time point, but there was no significant increase in this group at either 0 minutes post dose or at the end of study assessment, and there were no significant changes in systolic blood pressure in the AD group at any time point. No subjects experienced increases of more than 60 msec from baseline in QTc as calculated by either the Bazett or the Fridericia formulae at any time point during the study. No QTc values exceeded 500 msec at any time point during the study. The mean increase from baseline did not exceed 10 msec at any time point. No statistically or clinically significant changes in QTc were noted at the time of peak plasma concentration (immediately after injection) or at

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study end. However, a small, but statistically significant increase in QTc (4.2 msec by Bazett and 5.8 msec by Fridericia formulae), was noted 90 minutes post-administration.

Two subjects had changes in laboratory values that met the apriori criteria for being potentially clinically significant. Subject 012-006 had a hemoglobin of 11.4 g/dL at study end, down from 12.7 g/dL at baseline (hematocrit was 36% at both baseline and study end). Subject 012-021 had a urine specific gravity at study end of 1.005 down from 1.025 at baseline. Both values barely exceeded the threshold for potentially clinically significant; neither was considered clinically significant by the investigator.

While there were no changes that reached statistical significance in both the AD group and the control group, there were a number of changes in laboratory parameters that reached statistical significance in one group or the other. Most notable was a significant (p=0.0271) increase in serum glucose in the AD group (103.1 mg/dL pre-dose to 130.6 mg/dL post-dose) likely due to food consumption prior to the post-dose laboratory blood draw. The majority of the other changes that reached significance in this group post-dose (small changes in red cell indices and electrolyte levels) were attributable to the increased glucose level. In addition, subjects were encouraged to drink water (in order to facilitate voiding) prior to the post-dose laboratory blood draw, and small but significant changes in urine pH, urine specific gravity, blood urea nitrogen and serum uric acid were all seen. All of these changes are likely related to increased hydration. There was also a slight but statistically significant (p=0.0373) change in alkaline phosphatase (76.6 U/L pre-dose to 77.6 U/L post-dose) in the AD group only, and a slight but statistically significant change in WBC differential (% neutrophils decreased by approximately 2%) in the control group only. None of these changes appear to be clinically significant and none resulted in laboratory values that were outside of the normal reference range.

Radiation Dosimetry

Dosimetry analyses performed in the Group A subjects (012-004, 012-012 and 012-019) were consistent with the estimates derived from biodistribution studies in mice. The human effective dose was approximately 0.013 mSv/MBq or 4.81 mSv (481 mrem) for a 370 MBq (10 mCi) dose. The human effective dose equivalent (EDE) was approximately 0.019 mSv/MBq or 6.9 mSv (0.69 rem) for a 370 MBq (10 mCi) dose.

Clearance, Metabolism and Excretion

Clearance of ^{18}F-AV-45 from plasma was determined by obtaining 1 mL samples of venous (3 subjects) or arterial (2 subjects) at various time points following injection of 10 mCi (370 MBq) ^{18}F-AV-45. A 0.2-mL portion of the plasma fraction was counted in a gamma counter for total activity and plotted vs. time after correction for decay between collection and counting of samples. High-pressure liquid chromatography (HPLC) analysis of radioactive plasma samples was performed.

The total radioactivity cleared rapidly from plasma. Within 10 minutes of the injection, the total radioactivity was reduced by 80%. The radioactivity in plasma consisted of contributions from non-metabolized parent, ^{18}F-AV-45, and its metabolites. The amount of parent decreased with time generating 3 observable metabolites.

Arterial blood samples from 2 subjects (012-004 and 012-005) were further analyzed in an effort to characterize the metabolites of ^{18}F-AV-45. Chromatographic analysis revealed that ^{18}F-AV-45 is rapidly metabolized as well as rapidly cleared from circulation. In addition to the parent, ^{18}F-AV-45, the metabolite peaks from ^{18}F-AV-160 (desmethyl ^{18}F-AV-45), ^{18}F-AV-267 (N-acetyl ^{18}F-AV-160) and ^{18}F-polar species were observed. Of the metabolites observed, ^{18}F-AV-160 and ^{18}F-AV-267 have been characterized in preclinical studies. The identity of ^{18}F-polar has not been confirmed, but most likely it is

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generated upon the cleavage of the polyethylene glycol chain from ^{18}F-AV-45. This polar metabolite appears to be rapidly cleared and accounts for the majority of the radioactivity excreted in the urine.

Efficacy Results

A total of 16 healthy cognitively normal volunteers and 16 AD subjects were injected with ^{18}F-AV-45. One subject with AD, 023-006, withdrew consent after 5 minutes in the scanner, yielding no evaluable imaging data. Imaging technical failures occurred in 5 subjects. Four of the 5 technical failures occurred in AD subjects (023-002, 023-008, 026-006, and 026-011) and were due to excessive movement while in the scanner, which precluded proper attenuation correction and quantification of the results. The 5th subject (012-001), a healthy volunteer, was scheduled to be the first whole body biodistribution subject. Operational difficulties with the scanner precluded proper attenuation correction and reconstruction of the data, and no usable images were obtained from this subject. Thus, valid imaging data were available for a total of 15 controls and 11 subjects with AD.

Within 50 minutes of infusion, subjects with AD showed accumulation of ^{18}F-AV-45 in the frontal cortex, temporal cortex and precuneus areas (areas expected to be high in amyloid deposition), whereas healthy control subjects showed minimal accumulation of tracer in these regions. At this time point, ^{18}F-AV-45 had largely been cleared from the cerebellum (an area known to be free of amyloid plaques) in both AD subjects and control subjects. These differences were consistently evident in the ratio of standard uptake values (SUVR) in the target areas of the cortex relative to the cerebellum. Thus, the cortical average SUVR 50-60 minutes post administration of ^{18}F-AV-45 was 1.665 ± 0.175 for subjects with AD vs. 1.246 ± 0.177 for cognitively healthy controls.

Conclusions: Based on the efficacy assessments and results, it was demonstrated that the cortical brain regions of subjects with AD had higher uptake of ^{18}F-AV-45 over time compared with the brain regions of control subjects. The greatest increase in ^{18}F-AV-45 uptake occurred in the precuneus of AD subjects compared with control subjects. ^{18}F-AV-45 was shown to be well-tolerated and generally safe in the population studied.

Date of Report: 12 October 2009

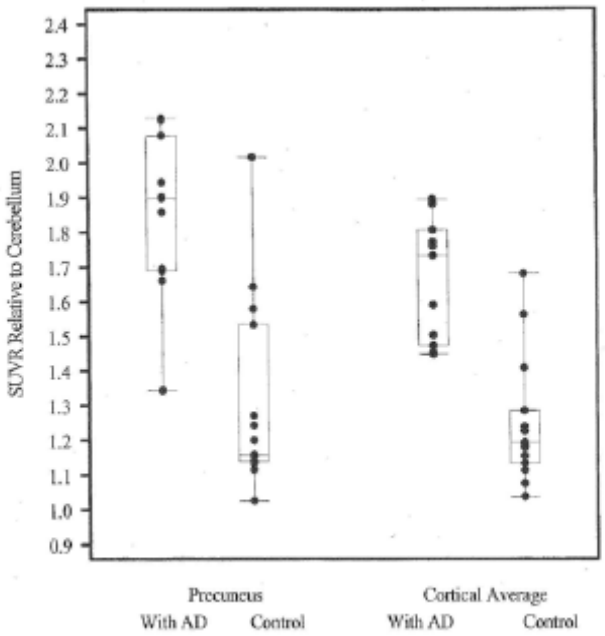
REVIEWER'S COMMENTS:

This Study (A01) failed to accurately calculate SUVRs (with respect to cerebellum). According to this Study, the PET images for 12 out of 15 healthy controls (cognitively normal) would be read as beta amyloid positive. This question was addressed to the sponsor on an information request sent on November 28, 2010. The sponsor acknowledged that they had inaccurately calculated SUVRs as they had included only part of cerebellum radioactivity rather than including whole cerebellum. According to the sponsor's new method 3 out 15 cognitively normal subjects gave beta amyloid positive images.

According to the results of this study (as calculated and reported by the sponsor in Study A01), most of the healthy controls would give a +ve image on PET scan. A positive image as defined by the sponsor is where SUVR >1.1. Thus according to the results of Study

Reference ID: 2904801

A01, 12 out of 15 cognitively normal subjects will yield a beta amyloid positive PET scan. This raised serious concerns regarding the clinical utility (to distinguish beta amyloid positive patients and beta amyloid negative subjects) of florbetapir-PET imaging.



Box diagram of SUVR vs precuneus/cortical averages in patients with AD and HC (Study A01)

An information request letter was sent to the sponsor from clinical pharmacology team. The information request (in bold) and sponsor's response is given below:

*"**The indication sought by Avid is, "A negative florbetapir-PET scan is useful in ruling out the presence of pathologically significant levels of beta amyloid in the brain." Therefore it becomes important that florbetapir-PET give "accurate true negative" scans for healthy volunteers. In Study A07, the pivotal trial, one of the clinical endpoint was to demonstrate the specificity of florbetapir. The population used for this trial was ages 18-40 years of age. The mean age was 26 years. The Study confirmed that 26 year old healthy volunteers do not have beta amyloid. The Company, however, has not demonstrated that florbetapir PET image can "effectively/accurately rule out beta amyloid" in healthy volunteers >50 years of age, the population where drug is indicated to be used.***

On the other hand, the data from Study A01 and A05 employed healthy volunteers with the age over 50 years. These studies show high numbers of "false positive" for healthy volunteers >50 years of age (MMSE >29) based on SUVR >1.1 as beta amyloid positive image using a visual binary read as proposed by Company. In Study A01, it appeared that 80 % of the healthy volunteers (i.e., 12 out of 15 healthy volunteers) have substantial levels of Beta-amyloids howed by PET image (Please refer to Figures

14.4.1.7 and Figure 14.5.1.5 for Study A01). Similarly, in Study A05, it appears that 22.8 % (i.e., 18 out of 79 healthy volunteers) of PET reads (based on visual binary reads) would be assessed as "positive".

The % of false positive read for Study A05 appears much better than Study A01. Please explain how nuclear medicine physician would accurately identify healthy volunteers based on florbetapir-PET scan with the high number of false positive image in healthy volunteers (i.e., 22.8 – 80 %).

Sponsor's Response: "Thank you for allowing us to clarify this issue. We do not consider the positive scans in cognitively normal elderly volunteers to be "false positives". Rather, the positive scans most likely represent cases of beta-amyloid pathology in individuals who are still functioning in the cognitively normal range. It is well documented in the Alzheimer's literature that substantial levels of beta-amyloid exist in ~20-30% of elderly subjects identified as cognitively normal, as detected by autopsy studies or by imaging studies (e.g., Price and Morris, 1999; also see ISE section 2.7.3.3.2.1.3.1, references 31-36). A large study using C11-PIB PET imaging of 242 cognitively normal subjects found a very similar percent of subjects with positive scans in the > 50 yr old healthy subjects and that the frequency of positive scans increases with age (Morris et al., 2010). Given the similarity of our data with the pathological results (and with other amyloid PET imaging data) we do not believe the positive florbetapir-PET scans in Study A05 are false positive scans, but rather represent asymptomatic brain amyloidosis, now thought by many to represent a preclinical state of AD (e.g. see the NIA/Alzheimer'sAssociation new proposed criteria for "Preclinical Alzheimer's disease" and also International Working Group criteria for "Preclinical states of AD" and "Asymptomatic at-risk state for AD") [Lancet Neurology, 2010]).

Given the well-known incidence of amyloid pathology in asymptomatic elderly controls, the Phase III specificity analysis focused only on young normal controls, in whom we could infer with high confidence the absence of amyloid pathology (based on literature data from autopsy series, e.g. Braak & Braak, 1997, and as suggested by the agency at the type C meeting response letter 06 Feb 2009).

Finally, as the agency has outlined and we agree, there is an important difference between
detection of significant amyloid pathology and diagnosis of Alzheimer's disease. This product indication focuses on the former (i.e. a molecular indication) not the later (i.e. a diagnostic indication). For a molecular indication, sensitivity and specificity can only be measured in subjects in whom the presence or absence of the target can be known with high confidence (i.e.,autopsy subjects and young cognitively normal controls).

Also, please explain the discrepancy in the results of two trials (A01 and A05).
The SUVR values in Study A01were calculated using different brain regions than the SUVR values in subsequent studies and a cut point of SUVR > 1.10 cannot be used for A01. The most important difference was that the reference region for Study A01 was cerebellar gray matter, whereas the whole cerebellum was used in later studies.

(Cerebellar gray matter has lower activity than the cerebellum as a whole and using the cerebellar gray matter made the Study A01 values higher, on average, than those from the later studies.) This change to using the whole cerebellum was made in the subsequent studies to improve the reliability of calculation.
As a consequence, the cut point of 1.10, proposed for later studies does not apply to the original A01 data. We note, however, that the A01 images were reanalyzed using the whole cerebellum reference region in Study A06. Study A06 Listing 14.8 lists the revised SUVR values for all subjects. Instead of 12 subjects, only 3 of 15 HC from study A01 had SUVR > 1.10. These were 012-003 (1.27, age 84), 012-006 (1.42, Age 84) and 012-020 (1.18, Age 80). These subjects were also read visually positive. This rate of positive HC (20%) is consistent with the rate in our other studies, including A05."

Thus Study A01 failed to calculate correctly the pharmacodynamic factors SUV for various target cortical region versus cerebellum. It was only realized later at the end of Phase II study that there were errors in calculating SUVR in Study A01.

2. For Study A01, please provide in excel spreadsheet the ages, corresponding MMSE scores, precuneus and cortical averages relative to cerebellum for all subjects in healthy volunteer group (N=16) and Alzheimer's Disease group (N=16). Also provide (for Study A05 subjects) in excel spreadsheet format the ages, corresponding MMSE scores, precuneus and cortical averages relative to cerebellum for all healthy subjects (N=79).

Sponsor's response: "As noted above, the original Study A01 SUVR data in the clinical study report are not comparable to data from subsequent studies due to the change in SUVR methodology during Phase II trials. However, the SUVR data from the A01 subjects that were re-analyzed in the Study A06 are comparable to SUVR results obtained in all Phase II and III studies. The precuneus SUVR values were not explicitly calculated in study A06, but the cortical average SUVR as well as the age of each subject, their MMSE values and the visual read score are in the A06 study report, Listing 14.8. Please note that the SUVR could not be calculated for all subjects in study A01 due to withdrawal from the study by 1 AD subject and technical issues for 4 AD and 1 HC. Data are available in Study A06 for 15 HC and 11 AD subjects enrolled in the A01 trial and analyzed by the final SUVR methodology used in Phase II and III trials. Comparable data from Study A05 are found in the study report listings 16.2.1.3, 16.2.1.12, and 16.2.3.3.

All of the above data are in the integrated database (including the original A01 SUVR data calculated with the Phase I methodology). An excel spreadsheet has been provided from the integrated database. Data from 78 healthy control subjects in A05 and 26 AD and healthy control subjects in A01 are included."
3. It is evident from Study A01 and A05 that the "load of beta amyloid" increases in healthy volunteers with age. Our preliminary analysis shows that due to higher beta amyloid loads in older (70 years and older) healthy volunteers, a higher number of "false positive" PET reads will be observed with visual binary PET reads. Please describe a correlation between age and beta amyloid by grouping healthy volunteers in two cohorts >50 to 69 and 70 years of age and older.

Age is a well-documented risk factor for both symptomatic Alzheimer's disease and for asymptomatic brain amyloidosis. Consistent with this, we report both the proportion of cognitively healthy subjects (HC) who are amyloid positive (Aβ+) on the PET scan blinded reader assessment, as well as the cortical average SUVR, increases with age".

Positron Emission Tomography Whole Body Biodistribution Using ^{18}F-AV-45

Protocol Number:	^{18}F-AV-45-A02
Phase:	1
Study Drug:	^{18}F-AV-45
Indication Studied:	Alzheimer's disease
Study Design:	Open-label, single center study evaluating the radiation dosimetry and safety of ^{18}F-AV-45 in 9 healthy subjects
First Subject Enrolled:	31 October 2007
Last Subject Completed:	04 January 2008
Sponsor:	Avid Radiopharmaceuticals, Inc
	Sponsor's Responsible Medical Officer: Daniel M. Skovronsky, MD, PhD
	Sponsor's Contact Person: Michael J. Pontecorvo, PhD Telephone: 215-966-6221 Fax: 413-826-0416
Report Date	04 November 2009

This study was performed in compliance with the principles of good clinical practice (GCP). The information contained in this Clinical Study Report is CONFIDENTIAL and the information contained within it may not be reproduced or otherwise disseminated without the approval of Avid Radiopharmaceuticals.

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals, Inc.	^{18}F-AV-45	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

Clinical Study Synopsis

Title: Positron emission tomography whole body biodistribution using ^{18}F-AV-45

Investigators: This study included one principal investigator.

Study Centers: This study was conducted at one study center.

Dates of Study: 31 October 2007 through 04 January 2008

Clinical Phase: Phase 1

Publications: None

Objectives: The primary objective of the study was to determine the whole body radiation dosimetry of ^{18}F-AV-45, an amyloid-targeted radiopharmaceutical, in healthy volunteers.

Methodology: This was an open-label, single-center study of ^{18}F-AV-45 in nine healthy subjects. Screening assessments were performed on Day 0 and included subject informed consent, demographic information, medical history, concomitant medications, physical and neurological examinations, clinical laboratory tests and safety assessment results (electrocardiogram [ECG], vital sign evaluation, and physician assessments). Subjects who met all study entry criteria were enrolled in the study and had a catheter placed in a vein in their arm for injection of ^{18}F-AV-45. Once the catheter was in place, the subject was positioned on the scanner bed and a whole body computed tomography (CT) scan was performed for attenuation correction and anatomic localization. After the CT scan and before positron emission tomography (PET) imaging, ^{18}F-AV-45 was injected through the injection catheter followed by a saline flush. PET scans from the vertex of the head to the thighs were repeated periodically over approximately 6 hours following injection. Electrocardiogram (ECG) and vital sign assessments were performed at the beginning and at the end of the study. Adverse events were monitored continuously throughout the study.

Number of Subjects Planned and Analyzed: A total of 10 healthy subjects were planned to participate in the study. Nine subjects were enrolled in the study; all nine subjects completed the study and were analyzed.

Diagnosis and Main Criteria for Inclusion: Healthy subjects who were between 18 and 85 years of age, provided informed consent, and were able to lie still on the imaging table for a period of up to one hour were eligible to participate in the study.

Reference ID: 2904801

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals, Inc.	^{18}F-AV-45	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

Dosage and Administration:

Test Product

Eligible subjects received a single intravenous (IV) dose injection of approximately 370 MBq (10 mCi) of ^{18}F-AV-45 in a volume of ≤ 10 mL of 0.5% sodium ascorbate (ascorbic acid and sodium salt), and 10% ethanol in normal saline.

Duration of Treatment:

^{18}F-AV-45: single IV-dose per subject

Criteria for Evaluation:

PET scan images: PET scan images were evaluated to provide the biodistribution and radiation dose values (millisievert/ megabecquerel [mSv/MBq]) for target organs, including the adrenals, brain, breasts, gall bladder wall, lower large intestine wall, small intestine wall, stomach wall, upper large intestine wall, heart wall, kidneys, liver, lungs, muscle, ovaries, pancreas, osteogenic cells, skin, spleen, testes, thymus, thyroid, urinary bladder wall, uterus, and total body.

Urine and enteric excretion fractions: Cumulative bladder activity measurements were used to model urinary excretion rates and activity that was not excreted in the urine was assumed to be eliminated in the feces. In addition, regions of interest (ROI) were used to establish the amount of activity in the intestines and gallbladder. The activity that entered the duodenum with the flow of bile was assumed to be transferred through the alimentary canal.

Safety: Safety was assessed by monitoring adverse events, vital sign assessments, and ECGs. Vital signs were measured before study drug administration, and 380 minutes after administration of ^{18}F-AV-45 and subjects underwent resting ECGs 10 minutes and 5 minutes before ^{18}F-AV-45 administration, and at 380 minutes after ^{18}F-AV-45administration.

Statistical Methods:

Subject disposition, demographics, and baseline characteristics were summarized using descriptive statistics. Whole body PET scans were obtained for all subjects who received a dose of ^{18}F-AV-45. Whole body images were reconstructed using a standard algorithm. Regions of interest (ROI) were manually drawn within the outer border of those organs that extract enough activity to be seen clearly on the images. Time-activity curves from the ROIs were fit to retention functions and integrated for use in calculating radiation dose estimates using standard methods. Radiation dose estimates were summarized using descriptive statistics.

Safety analyses were performed for all subjects who received a dose of study drug. Extent of exposure, treatment-emergent adverse events, vital sign assessments, and ECG results were summarized using descriptive statistics.

Sponsor:	**Name of Compound:**	**Active Ingredient(s):**
Avid Radiopharmaceuticals, Inc.	^{18}F-AV-45	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

Summary and Conclusions:

Radiation Dosimetry Results: Dosimetry results were reasonably consistent between the nine subjects. Most organs received between 0.005-0.03 mSv/MBq, but the liver, gallbladder, small intestine and upper large intestine received 0.06-0.14 mSv/MBq. The total body effective dose was 0.019 ± 0.004 mSv/MBq. Modeling urinary bladder voiding at 90 minutes post-injection did not significantly change the radiation dosimetry.

Safety Results: A total of 9 treatment-emergent adverse events were reported for 5 subjects during the study. The most common treatment-emergent adverse event was musculoskeletal pain, experienced by 3 subjects (33.3%). All treatment-emergent adverse events were mild or moderate in severity and were considered not related to ^{18}F-AV-45. No serious adverse events or deaths were reported during the study; none of the subjects discontinued the study because of an adverse event. No notable changes from baseline were observed for vital sign assessments or ECG results.

Conclusions: The imaging agent, ^{18}F-AV-45, was evaluated in healthy subjects to assess the safety and radiation dosimetry of this imaging agent. ^{18}F-AV-45, administered as a single IV injection of 370 MBq (10 mCi), was shown to be safe and well-tolerated in this population of healthy subjects. The maximum organ radiation dose observed in this study was 0.14 mSv/MBq for the gall bladder. The total body effective dose was 0.019 ± 0.004 mSv/MBq (approximately 7 mSv for a 370 MBq injection). Modeling urinary bladder voiding at 90 minutes post-injection did not significantly change the radiation dosimetry results.

Date of Report: 04 November 2009

Table 11-2 Radiation Dose Estimates (mSv/MBq administered)

	Average	SD
Adrenals	1.36E-02	1.29E-03
Brain	1.00E-02	1.86E-03
Breasts	6.24E-03	8.65E-04
Gallbladder Wall	1.43E-01	8.02E-02
LLI Wall	2.78E-02	1.02E-02
Small Intestine	6.55E-02	2.96E-02
Stomach Wall	1.17E-02	9.06E-04
ULI Wall	7.45E-02	3.42E-02
Heart Wall	1.31E-02	1.59E-03
Kidneys	1.30E-02	1.11E-03
Liver	6.44E-02	2.21E-02
Lungs	8.52E-03	8.01E-04
Muscle	8.63E-03	7.62E-04
Ovaries	1.76E-02	4.34E-03
Pancreas	1.44E-02	1.34E-03
Red Marrow	1.43E-02	1.78E-03
Osteogenic Cells	2.76E-02	3.71E-03
Skin	5.93E-03	8.09E-04
Spleen	8.90E-03	9.86E-04
Testes	6.81E-03	1.29E-03
Thymus	7.27E-03	1.22E-03
Thyroid	6.75E-03	1.43E-03
Urinary Bladder Wall	2.71E-02	1.17E-02
Uterus	1.56E-02	3.19E-03
Total Body	1.16E-02	9.51E-04
Effective Dose	**1.86E-02**	**4.26E-03**

Source: Dosimetry Report provided in Appendix 16.1.14.
MBq: megabecquerel; hr: hour; LLI: lower large intestine; mSv: millisievert; SD: standard deviation; ULI: upper large intestine.

An open label, parallel group, dose comparison of safety and imaging characteristics of 111 and 370 MBq (3 and 10 mCi) of ^{18}F-AV-45 for brain imaging of amyloid in healthy volunteers and patients with Alzheimer's disease (AD)

Protocol Number:	^{18}F-AV-45-A03
Phase:	1
Investigational Product:	^{18}F-AV-45
Indication Studied:	Alzheimer's disease
Study Design:	Open-label, multicenter study comparing 2 different doses of ^{18}F-AV-45 in 11 healthy volunteers and 9 subjects with Alzheimer's disease.
First Subject Enrolled:	17 March 2008
Last Subject Completed:	01 August 2008
Sponsor:	Avid Radiopharmaceuticals, Inc.
	Sponsor's Responsible Medical Officer: Daniel M. Skovronsky, MD, PhD
	Sponsor's Contact Person: Michael J. Pontecorvo, PhD Telephone: 215-966-6221 Fax: 413-826-0416
Report Date	09 February 2010 Final
Amended Report	Minor editoral changes were made to Section 9.7.8 of the report on 13 July 2010 (see Appendix 16.1.5 for details)

Sponsor: Avid Radiopharmaceuticals, Inc.	**Name of Compound:** ^{18}F-AV-45 for Injection	**Active Ingredient(s):** (*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

Title of Study: ^{18}F-AV-45-A03

An open label, parallel group, dose comparison of safety and imaging characteristics of 111 and 370 MBq (3 and 10 mCi) of ^{18}F-AV-45 for brain imaging of amyloid in healthy volunteers and patients with Alzheimer's disease (AD)

Test Product: ^{18}F-AV-45

Doses: 111 MBq (3 mCi) and 370 MBq (10 mCi)

Route of Administration: Intravenous (IV) bolus

Study Phase: 1

Study Centers: The study was conducted at 3 study centers: Clinical Research Institute (Site 124, Howard A Hassman, DO and Roberta R Ball, DO), Community Health Research (Site 226, Steven Edell, DO), and Premiere Research Institute (Site 322, Carl Sadowsky, MD).

Objectives:

The primary objectives of this study were to:

- Obtain additional information regarding the safety of ^{18}F-AV-45 in healthy volunteers and subjects with AD;
- Determine the appropriate dose of ^{18}F-AV-45 by comparing two doses (111 and 370 MBq [3 mCi and 10 mCi, respectively]) in both healthy volunteers and subjects with AD; and
- Obtain additional data for evaluation of the pharmacokinetics and metabolism of ^{18}F-AV-45.

Number of subjects (Enrolled):

A total of 20 subjects (9 AD subjects, 11 control subjects) were enrolled in the study. Nine subjects (5 AD, 4 control) and 11 subjects (4 AD, 7 control) were assigned to the 111 MBq (3 mCi) and 370 MBq (10 mCi) dose groups, respectively.

Eligibility:

Subjects with AD were enrolled if they:

- Were males or females > 50 years of age;
- Met the National Institute of Neurological and Communication Disorders and Stroke (NINCDS) criteria for probable AD and had a Mini Mental State Examination (MMSE) score at screening between 10 and 24 inclusive;
- Had a caregiver who could report on their mental status and activities of daily living; and
- Gave informed consent. If the subject was incapable of informed consent, the caregiver could consent on behalf of the subject (the subject still confirmed assent).

Healthy volunteers were enrolled if they:

- Were males or females ≥ 35 years of age and ≤ 55 years of age;

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- Had a MMSE score ≥ 29, and were cognitively normal on the psychometric test battery at screening; and
- Gave informed consent.

Subjects were excluded from enrollment if they:

- Had clinically significant neurologic disease (other than AD, as appropriate);
- Had a diagnosis of other dementing / neurodegenerative disease (eg, Parkinson's disease, dementia with Lewy bodies, Lewy body variant AD, etc.);
- Had a diagnosis of mixed dementia;
- Had evidence from magnetic resonance imaging (MRI) or other biomarker studies that suggested an etiology of dementia other than AD, or in the case of cognitively normal volunteers, had evidence from MRI or other biomarkers indicating presence of AD pathology;
- Had current clinically significant cardiovascular disease or clinically significant abnormalities on screening electrocardiogram (ECG) (including, but not limited to, QTc > 450 msec);
- Had current clinically significant psychiatric disease. Subjects with behavioral dysfunction in AD could be entered only after discussion and with the approval of the sponsor;
- Had a current clinically significant endocrine or metabolic disease, pulmonary, renal or hepatic impairment, or cancer;
- Had clinically significant infectious disease, including acquired immune deficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection or previous positive test for hepatitis B, hepatitis C, or HIV;
- Had a history of alcohol or substance abuse or dependence;
- Were taking medications known to cause QT-prolongation;
- Were women of childbearing potential who were not surgically sterile, not refraining from sexual activity, or not using adequate contraception, or were pregnant or lactating;
- Took sedating antihistamines within 48 hours of imaging, required medications with a narrow therapeutic window (eg, warfarin), were receiving any investigational medications, or had participated in a trial with investigational medications within 30 days of participating in this study. Treatment with psychotropic medication was not forbidden, but investigators were instructed to carefully consider whether subjects requiring psychotropic medications would be able to complete the imaging session;
- Had ever participated in an experimental study with an amyloid targeting agent (eg, immunotherapy, secretase inhibitor) unless it could be demonstrated that the subject received only placebo in the course of the trial. Subjects with AD could be on a stable dose of an anticholinesterase and/or Namenda, and could be taking vitamin E at the time of imaging. Other approved or over-the-counter (OTC) treatments for dementia (eg, ginkgo) were prohibited;
- Had a radiopharmaceutical imaging or template procedure within 7 days of the imaging session; or
- Had a body mass index (BMI) < 19 or > 32.

Study Design:

This study compared two different doses (111 MBq [3mCi] and 370 MBq [10 mCi]) of ^{18}F-AV-45 to determine the appropriate dose range for future studies. Nine subjects (5 AD, 4 control) were enrolled in the 111 MBq (3 mCi) dose group and 11 subjects (4 AD, 7 control) in the 370 MBq (10 mCi) dose group.

Reference ID: 2904801

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals, Inc.	^{18}F-AV-45 for Injection	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

Each subject was injected with a single IV bolus of either 111 or 370 MBq of ^{18}F-AV-45 and received a 90-minute continuous dynamic positron emission tomography (PET) scan. Adverse events and serious adverse events were collected continuously throughout the course of the study. A physician saw the subject at screening, before administration of ^{18}F-AV-45 and before discharge. Subjects who experienced an adverse event were not discharged until the event had resolved or stabilized.

Assessments and Endpoints:

Screening: Day 0

Screening assessments for all subjects included:

- Informed consent;
- Demographics (age, sex, education, alcohol and drug use, smoking);
- BMI calculation;
- Medical history, physical and neurological exam, concomitant medications;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of neurologic disease);
- Cognitive testing (MMSE, Alzheimer's Disease Assessment Scale [ADAS], Wechsler Logical Memory Score I and II, and verbal fluency);
- Safety (vital signs, ECG, clinical laboratory tests);
- Serum beta-human chorionic gonadotropin (β-hCG) test (female subjects);
- MRI (If an MRI had been performed within 6 months of screening and the results were available for possible use in normalizing regions of interest from the PET scan, the MRI was not repeated);
- A physician saw the subject during the screening visit.

Imaging: Day 1

The following assessments were performed for all subjects:

- Following administration of ^{18}F-AV-45, subjects had continuous brain PET imaging for 90 minutes;
- Vital signs were taken immediately before (within 5 minutes), immediately after (approximately 0 to 1 minutes), 90 minutes after (at completion of PET scanning), and approximately 120 minutes (at the end of study) after the injection of ^{18}F-AV-45;
- Three replicate ECGs were performed at 4 different time points on the imaging day: approximately 5 minutes before the injection of ^{18}F-AV-45, immediately after the injection, at completion of PET scanning (approximately 90 minutes after the injection), and at the end of study assessment (approximately 120 minutes after the injection);
- Venous blood samples were collected from 10 subjects (124-004, 124-005, 124-011, 124-015, 124-020; 124-021, 226-004, 226-005, 226-009, and 226-012) at various time points, and urine specimens were collected from 6 subjects (124-005, 124-011, 124-015, 124-020, 124-021, and 226-005) at 90 minutes for metabolite evaluation;
- Blood and urine samples were collected for clinical laboratory tests before the administration of ^{18}F-AV-45 and at the end of the study (approximately 120 minutes post-injection);
- Female subjects of childbearing potential received a pregnancy urine dipstick test before the injection of ^{18}F-AV-45;
- Subjects were observed continuously for signs of adverse events or serious adverse events;

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- The injection site was observed for excessive inflammation in or damage to the tissue surrounding where the dose was injected; and
- A physician saw the subject before discharge.

Follow-up

- A follow-up phone call to the subject (or caregiver as appropriate) was made approximately 7 days after imaging to confirm the subject's well-being and to collect information on any new adverse events.

Evaluation of Imaging:

Images were evaluated qualitatively:

- Images were visually examined by a nuclear medicine specialist who was blinded to the dose in order to determine whether the 3 and 10 mCi dose levels yielded acceptable image quality for reasonable subjective differentiation between AD and healthy subjects as well as to judge the overall image quality at each dose level;
- The optimal time window for visual discrimination of subjects with AD vs. healthy subjects (time from injection to proposed imaging in clinical use) was evaluated qualitatively for each dose condition; and
- Images were summed across varying durations to determine the minimum imaging duration to produce optimally evaluable images under each dose condition.

Images were also evaluated quantitatively:

- Peak regional uptakes and time-activity curves (Bq/cc) were calculated for cortical target areas and the cerebellum (reference region).
- Standardized uptake values (SUV) were calculated as a function of time, to produce a time-activity curve from 0 to 90 minutes post-administration for cortical target areas. SUV ratios (SUVR) for cortical target areas relative to cerebellum were also calculated;
- A global mean SUVR was calculated from the average across all cortical target areas; and
- The time of peak difference in SUV for the cortical target areas vs. cerebellum and the time of peak difference in SUVR were calculated for subjects with AD vs. healthy subjects.

Statistical Methods:

Demographic variables and cognitive scales were summarized using descriptive statistics for each group (AD and healthy subjects). Safety variables included adverse event count, clinical laboratory test results, vital signs measurements, and ECG results. Adverse events were summarized in terms of number and percentage of subjects experiencing an adverse event. For purposes of summarizing adverse events, only adverse events spontaneously reported to have occurred within 7 days of ^{18}F-AV-45 administration were reported. Any serious adverse events spontaneously reported to have occurred within 30 days of ^{18}F-AV-45 administration were reported. Clinical laboratory tests results, vital signs measurements and ECG results were summarized using descriptive statistics. End of study test results were compared to baseline test results using the paired t-test.

Image quality was assessed by a board-certified radiologist or nuclear medicine physician blinded reader for all subjects completing the study. For each region, the time activity curves and SUV/SUVR values were also summarized using descriptive statistics, as a function of time post injection for each group at each dose level. T-tests were used to compare regional SUVR between subjects with AD and healthy

Reference ID: 2904801

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subjects at the 50 to 60 minute time point. Mean values and variance within and across regions and time periods were also considered when comparing the two doses.

Results:

Subjects/Disposition

Twenty subjects were enrolled in this study; 9 subjects (5 with AD and 4 control subjects) received a single injection of 111 MBq (3mCi) and 11 (4 with AD and 7 control subjects) received 370 MBq (10 mCi) of ^{18}F-AV-45 followed by PET imaging. One of the AD subjects (322-003) at the 370 MBq level did not complete all the planned imaging time periods. For this subject all available data was included in the analysis. The mean age of AD subjects was greater than the control subjects in both the 370 MBq dose group (76.8 years vs. 45.0 years) and the 111 MBq dose group (74.8 years vs. 48 years). There were no significant differences in demographics between AD subjects in the 370 MBq and 111 MBq dose groups or between control subjects in both dose groups. The duration since onset of AD symptoms was longer in the 111 MBq dose group compared with the 370 MBq dose group (44 months vs. 25 months).

Efficacy Results

All 20 subjects had valid PET scan data and were included in the evaluable population. Standardized uptake values and SUVRs for target cortical brain regions were greater in subjects with AD compared with control subjects. The difference between AD subjects and control subjects was similar for both dose levels (111 MBq and 370 MBq). For both dose levels, the time activity curves show a clear separation between activity in cortical target areas and cerebellum (or centrum semiovale) in subjects with AD, but not in the control subjects, beginning around 15 minutes after dosing. Washout approached asymptote by 30 minutes and there was little change in SUVR values in either subjects with AD or controls between 30 and 80 minutes post injection of the 111 MBq and 370 MBq doses of ^{18}F-AV-45. There were no clinically significant differences in SUVR results for images acquired at time points between 30 and 90 minutes post-injection for either dose group for AD and control subjects, although the numerical optimum was observed between 40 and 70 minutes post-injection. Overall, visual assessments of the PET imaging quality for the 370 MBq dose were slightly better than the 111 MBq dose group. While all images were rated as "evaluable", visual assessments of the quality of the PET images revealed that 7 of 9 (80%) subjects in the 111 MBq group and 11 of 11 (100%) subjects in the 370 MBq group had quality ratings of ≥ 3 on a 5-point scale, where a score of 5 = excellent and 1 = poor. The visual differences in image quality; however, did not appear to affect the ability of the reader to identify high and low amyloid burden at the two dose levels: regional assessments of the frontal cortex, temporal cortex and precuneus revealed an assessment of high amyloid levels in 60% to 100% and 50% to 100% of AD subjects in the 111 MBq and 370 MBq dose groups, respectively, while an assessment of low to none was observed for 75% to 100% and 71% to 100% of control subjects in the 111 MBq and 370 MBq dose groups, respectively.

Overall, quantitative SUVR assessments of PET imaging results of the 111 MBq dose group were similar to those of the 370 MBq dose group. Mean SUVRs of target cortical areas relative to cerebellum were consistently higher in subjects with AD compared with those of control subjects, and in general mean SUVRs were comparable for the 111 MBq and 370 MBq dose groups. In AD subjects, mean SUVRs for the 111 MBq vs. the 370 MBq dose were 1.78 ± 0.22 vs. 1.66 ± 0.29, respectively (see Table 11-4), for the cortical average (average of frontal cortex, temporal cortex, precuneus, anterior cingulate, posterior cingulate, and parietal regions). In control subjects, mean SUVRs were for the 111 MBq vs. the 370 MBq dose were 0.97 ± 0.05 vs. 0.99 ± 0.09 for the cortical average, respectively. These SUVR results for the 111 MBq and 370 MBq dose groups were not significantly different (group-wise t-test, post hoc analysis on file at Avid Radiopharmaceuticals).

Reference ID: 2904801

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals, Inc.	^{18}F-AV-45 for Injection	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

Clearance, Metabolism and Excretion

The pharmacokinetics and metabolism of ^{18}F-AV-45 in 9 subjects enrolled in this trial were evaluated. Measurements of total ^{18}F radioactivity in blood as well as radio-high pressure liquid chromatography (HPLC) analysis of the plasma in this study showed that ^{18}F-AV-45 is rapidly cleared from circulation following intravenous bolus administration. The results showed an initial phase clearance half life ($t_{1/2}$) in blood of approximately 1 minute (accounting for clearance of 95% of the radioactivity by 20 minutes), and a slower terminal phase clearance $t_{1/2}$ of between 20 and 90 minutes representing a minor fraction (approximately 5%) of the administered ^{18}F radioactivity. No significant differences were observed in blood pharmacokinetic properties between healthy control and AD subjects in this study. By 20 minutes post-administration, approximately 5% of the injected ^{18}F dose remained in the blood and most of the ^{18}F remaining in circulation was in the form of metabolites of ^{18}F-AV-45. Each of the metabolites was present at low levels (< 2%) relative to the original ^{18}F injected dose after 5 minutes post-injection. The main radiolabeled components remaining in the blood after 20 minutes following administration to humans were a polar ^{18}F-metabolite (approximately 1.5% of injected dose), the parent ^{18}F-AV-45 (1.2%), and the desmethyl (N-demethylated) derivative, ^{18}F-AV-160 (approximately 1.0%). Given the low level of ^{18}F metabolites in circulation, the effect of the metabolites on the PET image of ^{18}F-AV-45 would be expected to be negligible. The very stable brain SUVR values observed in this study between 30 and 90 minutes after injection (Figure 11-6 and Figure 11-7) are consistent with the lack of impact of metabolites on brain imaging during this time period. All radioactivity in the urine was present as a polar metabolite of ^{18}F-AV-45. The results of this study are consistent with the initial human pharmacokinetics results from the ^{18}F-AV-45-A01 trial showing very rapid clearance of ^{18}F-AV-45 from circulation and minimal circulating metabolites after 10 minutes from dose administration (see Report TR-AV-45-027 in Appendix 16.1.13).

Safety Results

No serious adverse events or deaths were reported, and none of the subjects discontinued treatment because of an adverse event. Two (2) healthy control subjects in the 370 MBq group had treatment-emergent adverse events. Subject 124-004 experienced a mild burning sensation (injection site irritation) at the time of the injection. The event was considered probably related to administration of the imaging agent and resolved shortly after the injection stopped. Subject 124-008 had mild diarrhea and mild vomiting (approximately 4 hours after dose administration), which were considered unlikely related to ^{18}F-AV-45 injection and resolved within one day.

Although scattered shifts in hematology, chemistry, and urinalysis parameters were seen, no obvious trends were apparent. Several subjects had pre-dose to post-dose shifts into the abnormal range that included a hematocrit value in 1 AD subject (226-012) in the 111 MBq group, a hemoglobin value in 1 AD subject (226-004) in the 370 MBq group, and a urine specific gravity value in 1 control subject (124-015) in the 370 MBq group; however, these values barely exceeded the threshold for potentially clinically significant and were not considered of clinical importance.

Although a statistically significant increase in mean diastolic blood pressure was observed in the 370 MBq dose group at the 90-minute time point post-injection (immediately after the subjects finished the imaging procedure), the increase was not observed at the 120-minute time point post-injection. There were no other significant mean changes in vital signs measurements, including systolic blood pressure, heart rate and respiration rate in either the 111 MBq or 370 MBq dose groups. One AD subject (322-003) in the 370 MBq group had a systolic blood pressure measurement that was considered potentially clinical significant 90 minutes after injection of ^{18}F-AV-45. The pre-dose blood pressure measurement was not performed. The subject's systolic blood pressure measurements were 154 mmHg immediately after the injection and 186 mmHg at the 90-minute assessment. Vital signs measurements were not performed at the 120-minute assessment. There were no clinically significant changes in the subject's diastolic blood

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pressure (86 to 88 mmHg) or pulse rate (53 to 59 beats per minutes). A power failure occurred during this subject's imaging session and the stressful events may have contributed to the subject's elevated systolic blood pressure reading. The subject's screening blood pressure measurements and pulse rate were within normal limits: 120/70 mmHg and 55 beats per minute, respectively.

Statistically significant mean QTcB interval changes of 6.0 msec in AD subjects and 8.1 msec in control subjects were observed at 90 minutes after the administration of the 370 MBq dose; however, these same groups showed no statistically significant changes in QTcB at the immediate post-dose and 120-minute time points. There were no other significant changes in mean ECG parameter results following ^{18}F-AV-45 administration. Only one control subject (124-015) had a QTcB change > 30 msec, which increased from 390.0 msec at baseline to 425.0 msec, and was only seen at the 120 minutes post-injection time point, and not seen immediately after dose administration, suggesting that the observation was not likely related to administration of ^{18}F-AV-45. The QTcF baseline to 120 minute post-dose change was 24.0 msec. There was no clinically meaningful change in systolic blood pressure (114 to 124 mmHg), diastolic blood pressure (60 to 70 mmHg), or pulse (53 to 63 beats per minute) at any of the time points assessed.

Although fluctuations in laboratory parameters, vital sign measurements, and ECG measurements were observed during the study, none of these changes was identified as a safety issue of the investigational agent by the investigators.

Conclusions: The quantitative SUVR PET results of the 111 MBq (3 mCi) dose group were similar to those of the 370 MBq (10 mCi) dose group. The qualitative image read showed equivalent Aβ+ (amyloid positive) / Aβ- (amyloid negative) classification results at both doses. Overall, the visual evaluation of the images by the blinded reader showed that the image quality was slightly better in the 370 MBq (10 mCi) dose group relative to the 111 MBq (3mCi) group. ^{18}F-AV-45 was very rapidly cleared from circulation post-intravenous injection. Less than 5% of the injected ^{18}F radioactivity remained in blood by 20 minutes following administration, and essentially all of the ^{18}F was in the form of more polar metabolites of ^{18}F-AV-45. The stable brain SUVR image results were consistent with the lack of effect of these very low levels of metabolites in circulation over the imaging period of 30 to 90 minutes post-injection. All radioactivity in the urine was present as a polar metabolite of ^{18}F-AV-45. ^{18}F-AV-45 was shown to be well-tolerated in the population studied at both dose levels.

Date of Report: 09 February 2010 (Final)

Test-retest reproducibility of ^{18}F-AV-45 for brain imaging of amyloid in healthy volunteers and Alzheimer's disease patients

Protocol Number:	^{18}F-AV-45-A04
Phase:	I
Investigational Product:	^{18}F-AV-45
Indication Studied:	Positron emission tomography (PET) imaging of amyloid deposits in the brain
Study Design:	Open-label, multicenter study evaluating the test-retest reproducibility of amyloid imaging with ^{18}F-AV-45 by PET in 15 subjects with Alzheimer's disease and 10 healthy control subjects.
First Subject Enrolled:	22 April 2008
Last Subject Completed:	03 April 2009
Sponsor:	Avid Radiopharmaceuticals, Inc.
	Sponsor's Responsible Medical Officer: Daniel M. Skovronsky, MD, PhD
	Sponsor's Contact Person: Michael J. Pontecorvo, PhD Telephone: 215-966-6221 Fax: 413-826-0416
Report Date	14 July 2010 (Final)

This study was performed in compliance with the principles of good clinical practice (GCP). The information contained in this Clinical Study Report is CONFIDENTIAL and the information contained within it may not be reproduced or otherwise disseminated without the approval of Avid Radiopharmaceuticals.

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals, Inc.	^{18}F-AV-45 for Injection	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

Title of Study: ^{18}F-AV-45-A04

Test-retest reproducibility of ^{18}F-AV-45 for brain imaging of amyloid in healthy volunteers and Alzheimer's disease patients

Test Product: ^{18}F-AV-45

Doses: 370 MBq (10 mCi)

Route of Administration: Intravenous (IV) bolus

Study Phase: I

Study Centers: The study was conducted at 4 study centers: Institute for Neurodegenerative Disorders (Site 031, Danna Jennings, MD), MD Clinical (Site 138, Beth Safirstein, MD), Premiere Research Institute (Site 222, Carl Sadowsky, MD), and Community Health Research (Site 426, Steven Edell, DO).

Objectives:

The primary objectives of this study were to:

- evaluate test-retest reproducibility of ^{18}F-AV-45 for brain imaging of amyloid in healthy volunteers and subjects with Alzheimer's disease (AD);
- collect additional safety data on ^{18}F-AV-45 positron emission tomography (PET) imaging; and
- evaluate the effect of a slow vs. fast IV injection of ^{18}F-AV-45 in a subset (slow vs. fast bolus [SvFB] group) of AD subjects.

Number of Subjects (Enrolled):

A total of 25 subjects were enrolled: 21 subjects (11 subjects with AD and 10 healthy volunteers) were enrolled in the primary test-retest phase of the study, and an additional 4 AD subjects (SvFB group) were enrolled and dosed using a revised injection protocol to evaluate the effect of slow vs. fast IV injection.

Eligibility:

Subjects with AD were enrolled if they:

- Were males or females > 50 years of age;
- Met the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria for probable AD and had a Mini Mental State Examination (MMSE) score at screening between 10 and 24 inclusive;
- Had a caregiver who could report on their mental status and activities of daily living; and
- Gave informed consent. If the subject was incapable of informed consent, the caregiver could consent on behalf of the subject (the subject still confirmed assent).

Healthy volunteers were enrolled if they:

- Were males or females ≥ 35 years of age and ≤ 55 years of age;

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- Had a MMSE score $\geq$ 29, and were cognitively normal on the psychometric test battery at screening; and
- Gave informed consent.

Subjects were excluded from enrollment if they:

- Had clinically significant neurologic disease (other than AD, as appropriate);
- Had a diagnosis of other dementing / neurodegenerative disease (eg, Parkinson's disease, dementia with Lewy bodies, Lewy body variant AD, etc.);
- Had a diagnosis of mixed dementia;
- Had evidence from magnetic resonance imaging (MRI) or other biomarker studies that suggested an etiology of dementia other than AD, or in the case of cognitively normal volunteers, had evidence from MRI or other biomarkers indicating presence of AD pathology;
- Had current clinically significant cardiovascular disease or clinically significant abnormalities on screening electrocardiogram (ECG) (including but not limited to QTc > 450 msec);
- Were taking medications known to cause QT-prolongation;
- Had current clinically significant psychiatric disease. Subjects with behavioral dysfunction in AD could be entered only after discussion and with the approval of the sponsor;
- Had a current clinically significant endocrine or metabolic disease, pulmonary, renal or hepatic impairment, or cancer;
- Had clinically significant infectious disease, including acquired immune deficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection or previous positive test for hepatitis;
- Had a history of alcohol or substance abuse or dependence;
- Were women of childbearing potential who were not surgically sterile, not refraining from sexual activity, or not using adequate contraception or were pregnant or lactating;
- Took sedating antihistamines within 48 hours of screening, required medications with a narrow therapeutic window (eg, warfarin), were receiving any investigational medications, or had participated in a study with investigational medications within 30 days of study enrollment. Treatment with stable doses of psychotropic medication was not forbidden, but investigators were instructed to carefully consider whether subjects requiring psychotropic medications would be able to complete the imaging session;
- Had ever participated in an experimental study with an amyloid targeting agent (eg, immunotherapy, secretase inhibitor) unless it could be demonstrated that the patient received only placebo in the course of the study. Subjects with AD could be on a stable dose of an anticholinesterase and/or Namenda, and could be taking Vitamin E at the time of imaging. Other approved or over-the-counter treatments for dementia (eg, Ginkgo) were prohibited; or
- Had a radiopharmaceutical imaging or treatment procedure within the 7 days before the imaging session for this study.

Study Design:

Study ^{18}F-AV-45-A04 evaluated test-retest reproducibility of amyloid imaging with ^{18}F-AV-45. Fifteen AD subjects and 10 healthy control subjects were enrolled in this study. Screening assessments could take place over several days and included obtaining demographic information, cognitive testing, safety

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assessment, and an MRI scan. Subjects who qualified for the study returned to the clinic for a second imaging session within 4 weeks of the initial imaging session.

At each imaging session, subjects were injected with a single IV bolus of 370 MBq (10 mCi) of ^{18}F-AV-45. Approximately 50 minutes after the injection of ^{18}F-AV-45, the subject received a 20 minute continuous dynamic PET scan. Vital signs and ECG were obtained immediately before and immediately after the injection and upon completion of the imaging session.

Blood and urine samples for clinical laboratory tests were collected before the injection of ^{18}F-AV-45 and upon completion of each imaging session. Adverse events were monitored continuously during each imaging session and subjects were queried at the second imaging session to elicit any adverse events that may have occurred between the two imaging sessions. Subjects who experienced an adverse event were not discharged until the event had resolved or stabilized. A follow-up phone call to the subject (or the caregiver as appropriate) was conducted approximately 7 days after the last imaging session to confirm the well-being of the subject and to collect information on any new adverse events.

In a subset of 4 AD subjects (SvFB group), the procedure for IV dose administration was varied between the first and second imaging session such that a rapid bolus (< 5 second injection, with immediate flush) was given at one imaging session, and a slow bolus (approximately 20 to 30 second injection with a flush delayed by 10 seconds after dose administration) was given at the other imaging session.

Images were evaluated both qualitatively and quantitatively. For the qualitative image evaluation, the kappa statistic was calculated for the agreement of the blinder reader's interpretation of the test and retest scans. The intraclass correlation between the SUV ratios (SUVR) for the 2 scans was determined for the quantitative image evaluation.

Assessments and Endpoints:

Screening: Day 0

Screening assessments for all subjects included:

- Informed consent;
- Demographics (age, sex, education, alcohol and drug use, smoking);
- Medical history, physical and neurological exam, concomitant medications;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of AD, stroke or other dementing disorder);
- Cognitive testing (MMSE, Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog), Wechsler Logical Memory Score I and II, and verbal fluency);
- Safety (vital signs, ECG, clinical labs);
- Serum beta-human chorionic gonadotropin (β-hCG) test (female subjects);
- MRI (if an MRI had been performed within 6 months of screening and the results were available for possible use in normalizing regions of interest from the PET scan, the MRI was not repeated);
- A physician saw the subject during the screening visit.

Imaging: Day 1

The following assessments were performed for all subjects:

- Approximately 50 minutes after the administration of ^{18}F-AV-45, subjects had continuous brain PET imaging for 20 minutes;
- Vital signs were taken immediately before (within 5 minutes), immediately after (approximately 0 to

1 minute), and at the end of study (approximately 90 minutes after) the injection of ^{18}F-AV-45);

- ECGs (two replicates) were performed approximately 5 minutes before and immediately after dosing, and after completion of the imaging session;
- Blood and urine samples were collected for clinical laboratory tests before the administration of ^{18}F-AV-45 and at the end of the imaging session;
- Female subjects of childbearing potential received a pregnancy urine dipstick test before the injection of ^{18}F-AV-45;
- Subjects were observed continuously for signs of adverse events or serious adverse events;
- The injection site was observed for excessive inflammation in, or damage to, the tissue surrounding where the dose was injected; and
- A physician saw the subject prior to discharge.

Imaging: Day 2

- Subjects were queried regarding adverse events that occurred between the two imaging days.
- All other assessments were conducted as on Imaging Day 1.

Follow-up

- A follow-up phone call to the subject (or caregiver as appropriate) was made approximately 7 days after the final imaging session to confirm the subject's well-being and to collect information on any new adverse events.

Evaluation of Imaging:

Qualitative Evaluation of Brain PET Images

Images for qualitative evaluation were visually examined by a neuroradiology specialist who was blinded to the subject diagnosis and whether the images were test or retest images. The reader was trained using images selected from prior studies. The reader was blinded to clinical information and the images were presented in random order. For this qualitative evaluation, the reader classified the images as either Aβ+ (amyloid positive) or Aβ- (amyloid negative). In addition, the reader provided a visual semi-quantitative reading of the PET scans. The reader rated each image for overall cortical amyloid burden using a 5-point scale, ranging from 0 (no amyloid) to 4 (high levels of amyloid deposition). The reader supported the ratings by documenting objective image features that were judged to be present, including both regional ratings of amyloid deposition and whole-brain features.

Quantitative Evaluation of Brain PET Images

Images were evaluated quantitatively using an automated process to extract estimates of tracer retention from prespecified standard volumes of interest. PET imaging scans were processed to provide SUVs for the following target cortical regions: frontal cortex, temporal cortex, precuneus, anterior cingulate, posterior cingulate, parietal cortex, and cortical average (calculated as the average of the previous 6 regions), as well as several other brain regions including the centrum semiovale and cerebellum, which were designated as reference regions. In addition, SUVRs (SUV ratios relative to cerebellum or centrum semiovale) were determined for the above 6 regions.

Reference ID: 2904801

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Intrasubject test/retest variability

The intrasubject test/retest variability was assessed using the SUVR (relative to cerebellum and relative to centrum semiovale) from the retest imaging scan result relative to the test imaging scan result. This was computed as the absolute value of the percent difference between Retest (R) and Test (T) for SUVR values (Test/Retest (%) = Absolute ((R-T)/T)*100). The intrasubject test-retest variability was determined for each brain region.

Statistical Methods:

Demographic variables and cognitive scales were summarized using descriptive statistics for each group (AD and healthy subjects). Safety variables included adverse event counts, clinical laboratory test results, vital signs measurements, and ECG results. Comparisons were generally made to baseline, as appropriate. Descriptive statistics were used to detect changes within a cohort or differences between cohorts. Adverse events were summarized in terms of number and percentage of subjects experiencing an adverse event. For purposes of summarizing adverse events, only adverse events spontaneously reported to have occurred within 7 days of administration of ^{18}F-AV-45 were reported. Any serious adverse events spontaneously reported to have occurred within 30 days of the dose of ^{18}F-AV-45 were reported.

Images were evaluated both qualitatively using a kappa statistic for agreement of the qualitative interpretation (Aβ+ vs. Aβ-) as well as the semi-quantitative rating of amyloid burden (0-4) between the first and second scan, and quantitatively using an intraclass correlation between the estimated regional SUV/SUVRs for the 2 PET scans.

Results:

Subjects/Disposition

Fifteen subjects with AD and 10 healthy volunteers (control subjects) qualified for the study. Of the 25 subjects enrolled, 24 (14 AD and 10 control subjects) were imaged on 2 separate days not more than 4 weeks apart, and received a single IV dose of 370 MBq (10 mCi) of ^{18}F-AV-45 at each imaging session. One AD subject discontinued from the study. This subject was injected, however technical issues with the scanner prevented imaging on test day, and the subject was only evaluated for safety. Without a baseline scan, retest imaging was not required and the subject was discontinued from the study. Therefore, this subject was included in the safety population, but not in the evaluable population. A subset of 4 AD subjects (SvFB group) received a rapid bolus (< 5 second injection, with immediate flush) of ^{18}F-AV45 at the first imaging session, and a slow bolus (approximately 20 to 30 second injection with a flush delayed by 10 seconds after dose administration) at the second imaging session. The mean MMSE score was 29.7 and 20.7 for control and AD subjects, respectively.

Efficacy Results

Efficacy analyses were performed on a total of 24 subjects: 10 AD subjects, 10 cognitively healthy volunteers (controls), and the subset of 4 AD subjects who were enrolled to better understand the slow versus rapid (fast) administration procedure. However, due to poor subject positioning that resulted in an incomplete brain image on the retest image day, accurate quantitative analysis for healthy control Subject 031-004 was not possible. This control subject was excluded from the SUVR-based test-retest analyses, but was included in the qualitative results.

Both the SUVs and SUVRs were highly reproducible between test and retest image results for AD and control subjects whether comparing the 10-minute (50 to 60 minutes post-injection) or 20-minute (50 to 70 minutes post-injection) scans. SUVRs for the cortical average relative to cerebellum of test vs. retest 20-minute scans were 1.42 ± 0.25 vs. 1.41 ± 0.27 for AD subjects and 1.00 ± 0.06 vs. 1.01 ± 0.06 for

control subjects. The same reproducible trend was observed when the centrum semiovale was used as the reference instead of the cerebellum.

The rate of dose administration (slow vs. fast bolus injection) did not significantly alter the SUVR results for the 4 AD subjects (SvFB group) in which the rate of injection was varied (1.58 ± 0.31 vs. 1.68 ± 0.41).

The cortical average SUVRs showed good ICCs. The ICCs for cortical average SUVR with either cerebellum or centrum semiovale as a reference region between test and retest was 0.99 for AD subjects and 0.96 for control subjects Many regions also showed highly reproducible results. The regional ICCs for SUVR with cerebellum as a reference region between test and retest images ranged from 0.97 to 0.99 for AD subjects and 0.82 to 0.98 for control subjects for cortical brain regions during the 50 to 70-minute PET imaging period after injection of ^{18}F-AV-45. The ICCs for AD subjects and for control subjects were comparable during the 50 to 70-minute and the 50 to 60-minute time periods.

Intrasubject test-retest variability for cortical average SUVR (cerebellum) over the 50 to 70-minute time period was 2.4% for AD subjects and 1.5% for controls. Across cortical target regions, intrasubject variability ranged from 2.3% to 3.3% in AD subjects and from 1.4% to 2.9% in controls. Similar results were observed for the 50 to 60-minute time period. In control subjects, the test-retest variability for cortical average SUVR was 1.5% and 1.4%, respectively, for the 50 to 70 and 50 to 60-minute time periods. In the subset of AD subjects with available data at both time periods the variability was 1.5% and 1.9%, respectively, for the 50 to 70 and 50 to 60-minute time periods. This supports the use of the 50 to 60-minute as a highly reliable time period for quantifying the amyloid burden, and there is no additional gain in reliability and reproducibility with longer imaging times.

For the qualitative assessment of the images, the overall kappa statistic for the blinded reader agreement for Aβ+ or Aβ- classification of test and retest images is 0.89 (95% CI: 0.69, 1.0) for combined AD and control subjects (n=20). For the 10 control subjects, the kappa statistic for agreement between test and retest images was 1.00 (95% CI: 1.00; 1.00). Control subject images were read as Aβ- for all 10 test images and all 10 retest images. For the 10 AD subjects (not including the 4 SvFB AD subjects), the kappa statistic was 0.74 (95% CI: 0.26; 1.00) . One AD subject was read as Aβ+ on the test image and Aβ- on the retest image. All other AD subjects (9 of 10) were read the same on the test and retest images. The weighted kappa statistic for the blinded reader semi-quantitative rating of amyloid burden was 0.86 (95% CI: 0.77, 0.96) for combined AD and control subjects (n=20).

Safety Results

No serious adverse events or deaths were reported during the study and none of the subjects discontinued from the study because of an adverse event. Two subjects (1 AD subject, 1 control subject) had adverse events during the study. One AD (031-003) subject experienced 2 adverse events (supraventricular extrasystoles and ventricular extrasystoles), both events were mild in nature and considered remotely (unlikely) related to administration of ^{18}F-AV-45. One control subject (222-006) reported dysgeusia/metallic taste immediately after dose administration on both the test and retest day. This event was mild in nature and considered probably related to administration of ^{18}F-AV-45.

Although scattered shifts in clinical laboratory values from within the normal reference range to above or below the normal reference range were observed, no obvious trends related to administration of ^{18}F-AV-45 were apparent. A few subjects had laboratory values that were considered potentially clinically significant by predefined criteria. Two control subjects (031-004 and 031-009) had hematocrit levels that were considered potentially clinically significant (defined as ≤ 37%) during the study. Subject 031-004 had a baseline hematocrit of 39% that decreased to 37% at the post-dose assessment of the retest imaging day (screening: 37%; test day: pre-dose 39%, post-dose 39%). Subject 031-009 had a baseline hematocrit of 41% that decreased to 37% at the post-dose assessment of the retest imaging day (screening: 40%; test day: pre-dose 40%, post-dose 39%). One AD subject (138-004) and 1 control subject (222-005) had

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cholesterol levels that were considered potentially clinically significant (defined as ≥ 300 mg/dL) during the study. Subject 138-004 had a baseline cholesterol level of 288 mg/dL that increased to 310 mg/dL at the post-dose assessment on the retest imaging day (screening: 285 mg/dL; test day: pre-dose 314 mg/dL, post-dose 314 mg/dL). Subject 222-005 had a baseline cholesterol level of 294 mg/dL that increased to 301 mg/dL at the post-dose assessment on the retest imaging day (screening: 317 mg/dL; test day: pre-dose 270 mg/dL, post-dose 298 mg/dL). Five AD subjects (031-003, 031-011, 138-002, 222-007, and 426-005) and 3 control subjects (031-004, 031-006, and 031-007) had low urine specific gravity measurements that were considered potentially clinically significant (defined as ≤ 1.005). One subject had a post-dose specific gravity result of 1.003, 2 subjects had a result of 1.004, and the remaining 5 subjects had a result of 1.005. Most of these clinical laboratory values were near the threshold of potential clinical significance and were not considered related to administration of ^{18}F-AV-45.

There were no significant mean changes from baseline to post-dose systolic and diastolic blood pressure measurements. One AD subject (031-003) had a post-dose systolic blood pressure measurement that was considered potentially clinically significant. Subject 031-003 had a baseline systolic blood pressure of 150 mmHg that increased to 199 mmHg at the 90-minute post-dose assessment on the retest day; however, this subject had a screening systolic blood pressure of 151 mmHg and a test day pre-dose systolic blood pressure of 172 mmHg suggesting that the high systolic blood pressure values were not related to administration of ^{18}F-AV-45.

There were no consistent clinically significant changes from baseline ECG parameters. Neither the AD group nor the control group showed a statistically significant increase in QTcB or QTcF on the test or retest day at the peak plasma time point (immediate post-dose). The AD group, but not the control group, showed a statistically significant 6.0 msec increase in QTc as calculated by Fredericia (QTcF) approximately 90 minutes post-dose on the test day, and this group also showed a non-significant increase on the retest day (mean change, 1.9 msec). The control group showed a statistically significant 7.1 msec increase in QTcF on the retest day at the 90 to 95-minute time point, but not on the test day (2.4 msec). No significant changes occurred in QTcB. No individual subjects showed a mean increase in QTcB or QTcF > 30 msec or an absolute value exceeding 500 msec at any timepoint.

Although fluctuations in clinical laboratory values, vital signs measurements and ECG measurements and a few potentially clinical significant values were observed during the study, these values were usually observed on only one of the test days or were similar to baseline values. None of the changes in laboratory values, vital signs measurements or ECG measurements were considered related to ^{18}F-AV-45 administration.

Conclusions: The ^{18}F-AV-45 PET scan was highly reproducible at both the 50 to 60-minute time period as well as the 50 to 70-minute time period. Very good agreement (kappa > 0.85) between test and retest scans was confirmed on the visual read for both the qualitative (Aβ+/Aβ-) and semi-quantitative (0-4) amyloid burden scores. A very high intraclass correlation (> 0.95) and low test-retest variability (< 5%) were observed for all of the quantitative image assessments (SUVRs), and specifically, the cortical average SUVR was highly reproducible in all subjects (test-retest variability < 2.5%). Both the SUVs and SUVRs were highly reproducible between test and retest image results for AD and control subjects. ^{18}F-AV-45 PET scan results were not significantly altered by the rate of dose administration (slow vs. fast bolus injection). No clinically significant safety issues were identified with the administration of ^{18}F-AV-45 in the population studied.

Date of Report: 14 July 2010 (Final)

Reviewer's comment:
The study is acceptable from a clinical pharmacology perspective.

Reference ID: 2904801

An open label, parallel group, multicenter study, evaluating the safety and imaging characteristics of ^{18}F-AV-45 in healthy volunteers, patients with mild cognitive impairment (MCI) and patients with Alzheimer's disease (AD)

Protocol Number:	^{18}F-AV-45-A05
Phase:	II
Study Drug:	^{18}F-AV-45 (florbetapir F 18)
Indication Studied:	Alzheimer's disease
Study Design:	Open-label, parallel-group, multicenter study to expand the database of ^{18}F-AV-45 in 80 cognitively normal subjects, 40 subjects with Alzheimer's disease, and 60 subjects with mild cognitive impairment.
First Subject Enrolled:	12 June 2008
Last Subject Completed:	11 December 2008
Sponsor:	Avid Radiopharmaceuticals, Inc
	Sponsor's Responsible Medical Officer: Daniel M. Skovronsky, MD, PhD
	Sponsor's Contact Person: Michael J. Pontecorvo, PhD Telephone: 215-966-6221 Fax: 413-826-0416
Report Date	30 July 2010

This study was performed in compliance with the principles of good clinical practice (GCP). The information contained in this Clinical Study Report is CONFIDENTIAL and the information contained within it may not be reproduced or otherwise disseminated without the approval of Avid Radiopharmaceuticals.

Sponsor: Avid Radiopharmaceuticals, Inc.	**Name of Compound:** ^{18}F-AV-45 for Injection (florbetapir F 18)	**Active Ingredient(s):** (*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)
Title of Study: ^{18}F-AV-45-A05 An open label, parallel group, multicenter study, evaluating the safety and imaging characteristics of ^{18}F-AV-45 in healthy volunteers, patients with mild cognitive impairment (MCI) and patients with Alzheimer's disease (AD)		
Test Product: ^{18}F-AV-45 **Dose:** 370 megabecquerel (10 mCi) **Route of Administration:** Intravenous (IV) bolus		
Study Phase: II		
Study Centers: The study was conducted at 24 study centers.		

Objectives:
The primary objectives of this study were to:
• Expand the safety database of ^{18}F-AV-45 positron emission tomography (PET) imaging.
• Expand the database of ^{18}F-AV-45 PET imaging in cognitively normal subjects to:
  • Refine the definition of a negative scan;
  • Determine the rates of Aß positivity by PET imaging as a function of age in cognitively normal subjects.
• Expand the database of ^{18}F-AV-45 PET imaging in AD subjects to:
  • Refine the definition of a positive scan in subjects with AD;
  • Test if ^{18}F-AV-45 PET imaging yields the expected rates of positive scans in AD subjects based on historical autopsy data;
  • Test if ^{18}F-AV-45 PET imaging yields the expected pattern of regional distribution of Aß positivity in AD subjects, based on historical autopsy data.
• Evaluate the results of ^{18}F-AV-45 PET imaging in subjects with MCI in order to:
  • Determine how the prevalence of Aß positivity by PET imaging in this population compares with the prevalence in subjects with AD;
  • Understand how imaging characteristics and prevalence of Aß positivity vary in different subsets of subjects with MCI (eg, amnestic versus nonamnestic MCI).		

Number of subjects (Enrolled): A total of 184 subjects (45 subjects with AD, 60 subjects with MCI, and 79 cognitively normal subjects) were enrolled in the study.		

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Eligibility:

Inclusion Criteria

Subjects who met all of the following criteria were eligible to enroll in the arm of this study reserved for subjects with AD:

1. Male or female subjects at least 50 years of age, with probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (McKhann et al. 1984).
2. Subjects with mild/moderate dementia as evidenced by a Mini-Mental State Examination (MMSE) score ranging from 10 to 24, boundaries included, at screening.
3. Subjects whose history of cognitive decline had been gradual in onset and progressive over a period of at least 6 months. Evidence was present indicating sustained memory deterioration in an otherwise cognitively normal subject, plus additional impairment in another cognitive function such as: orientation, judgment and problem solving, or functioning in personal care.
4. Subjects who lived with or had regular visits from a responsible caregiver willing to provide information about the subject's cognitive status.
5. Subjects who signed an Institutional Review Board (IRB)-approved informed consent document (ICD) before any study procedures were performed. If the subject was incapable of informed consent, the caregiver consented on behalf of the subject (the subject still confirmed assent).

Subjects who met all of the following criteria were eligible to enroll in the arm of this study reserved for subjects with MCI:

1. Male or female subjects at least 50 years of age.
2. Subjects with complaint of memory or cognitive decline corroborated by an informant.
3. Subjects with a clinical dementia rating (CDR) of 0.5.
4. Subjects with objective cognitive impairment or marginally normal cognition with a documented history of high cognitive performance.
5. Subjects had no obvious causes for their cognitive impairment (eg, onset coincided with recent head trauma or stroke).
6. Subjects had sufficiently preserved general cognition and functional performance such that a diagnosis of AD could not be made at the time of the screening visit.
7. Subjects with essentially normal Alzheimer's Disease Clinical Studies Consortium Activities of Daily Living (ADCS ADL) Scale score.
8. Subjects who were not demented.
9. Subjects with an MMSE score >24.
10. Subjects who were presenting for initial diagnosis of cognitive impairment or who had presented for initial diagnosis of cognitive impairment within the past year.
11. Subjects who lived with or had regular visits from a responsible caregiver willing to provide information about the subject's cognitive status.
12. Subjects who signed an IRB-approved ICD before any study procedures were performed.

Subjects who met all of the following criteria were eligible to enroll in the arm of this study reserved for cognitively normal subjects:

1. Male or female subjects at least 50 years of age.
2. Subjects who had an MMSE score ≥29 and were cognitively normal based on history and psychometric test battery at screening.

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3. Subjects who lived with or had a reliable person who could verify their cognitive status.
4. Subjects who signed an IRB-approved ICD before any study procedures were performed.

Exclusion Criteria

Subjects with any of the following criteria were ineligible to enroll in this study:

1. Subjects with a documented diagnosis of MCI for greater than one year.
2. Subjects with neurodegenerative disorders other than AD, including but not limited to Parkinson's disease, Pick's disease, frontotemporal dementia, Huntington chorea, Down syndrome, Creutzfeldt-Jacob disease, normal pressure hydrocephalus, and progressive supranuclear palsy.
3. Subjects who had a past or current diagnosis of other dementing or neurodegenerative disease (eg, Parkinson's disease dementia, dementia with Lewy bodies, Lewy body variant AD).
4. Subjects who had a past or current diagnosis of mixed dementia.
5. Subjects who had cognitive impairment resulting from:
   a. Acute cerebral trauma or posttraumatic brain injury, subdural hematoma, or injuries secondary to chronic trauma (eg, sequelae from boxing);
   b. Hypoxic cerebral damage regardless of etiology; eg, cognitive or neurological deficits resulting from cardiac arrest or cardiac surgery, anesthesia, or severe self-poisoning episode, secondary to severe hypovolemia (orthostatic hypotension did not lead to exclusion);
   c. Vitamin deficiency states documented by medical history, such as folate, vitamin B_{12}, and other B complex deficiencies (eg, thiamine deficiency in Korsakoff's syndrome). (Note: subjects who took regular B_{12} and folate were not necessarily excluded);
   d. Cerebral infection including abscess, syphilis, meningitis, encephalitis, or AIDS;
   e. Primary or metastatic cerebral neoplasia;
   f. Significant endocrine or metabolic disease (eg, thyroid, parathyroid, or pituitary disease, Cushing syndrome, or severe renal failure);
   g. Mental retardation.

   Before enrolling a subject with past or current history of any of the above conditions, the investigator contacted the sponsor to discuss whether the condition could have contributed to the cognitive impairment.
6. Subjects who had clinically significant infarct or possible multi-infarct dementia as defined by the National Institute of Neurological and Communicative Disorders and Stroke criteria, including:
   a. A history of a significant cerebrovascular event resulting in a physical or neurological deficit that could confound the assessment of the subject's intellectual function;
   b. Multiple focal signs on neurological examination indicative of multiple ischemic episodes;
   c. One or more of the following findings on a magnetic resonance imaging (MRI) scan:
      - Multiple (2 or more) infarcts or white matter lacunes;
      - A single large infarct or a strategically placed infarct in the angular gyrus, the thalamus, the basal forebrain, the posterior cerebral artery or anterior cerebral artery territory;
      - Extensive periventricular white matter disease. Leukoaraiosis is common in normal individuals and subjects with AD. White matter deterioration should not have resulted in exclusion unless it was abnormal and widespread, eg, Binswanger disease.
7. Subjects who had any evidence on screening MRI, computed tomography (CT), or other biomarker studies that suggested an alternate etiology (other than probable AD in subjects with AD) for cognitive deficit; or in the case of cognitively normal controls, any evidence on screening MRI, CT, or other biomarker studies that suggested the presence of AD pathology.
8. Subjects who had current clinically significant psychiatric disease, as judged by the Diagnostic

and Statistical Manual of Mental Disorders, 4th edition criteria, particularly current major depression or schizophrenia. Subjects with dementia who were experiencing behavioral disturbances that required treatment with psychotropic medications could be entered only after discussion and with the approval of the sponsor. The investigator and sponsor were to carefully consider whether subjects with behavioral dysfunction would be able to complete the imaging visit.

9. Subjects with a history of epilepsy or convulsions, except for febrile convulsions during childhood.
10. Subjects who had clinically significant hepatic, renal, pulmonary, metabolic, or endocrine disturbances.
11. Subjects who had current clinically significant cardiovascular disease. Clinically significant cardiovascular disease usually included one or more of the following:
    a. Cardiac surgery or myocardial infarction within the last 6 months;
    b. Unstable angina;
    c. Coronary artery disease that required an increase in medication within the last 3 months;
    d. Decompensated congestive heart failure;
    e. Significant cardiac arrhythmia or conduction disturbance, particularly those resulting in atrial or ventricular fibrillation, or causing syncope, near syncope, or other alterations in mental status;
    f. Severe mitral or aortic valvular disease;
    g. Uncontrolled high blood pressure;
    h. Congenital heart disease; or
    i. Clinically significant abnormal result on electrocardiogram (ECG), including but not limited to corrected QT interval (QTc) >450 ms.

    Before enrolling a subject with any of the above conditions, the investigator had to contact the sponsor.
12. Subjects with a history of drug or alcohol abuse within the last year, or prior prolonged history of abuse.
13. Subjects who had clinically significant infectious disease, including AIDS or human immunodeficiency virus infection or previous positive test for hepatitis.
14. Women of childbearing potential who were not surgically sterile, not refraining from sexual activity, or not using reliable methods of contraception. Women of childbearing potential could not have been pregnant (negative serum beta-human chorionic gonadotropin [β-hCG] at the time of screening and negative urine β-hCG on the day of imaging) or lactating at screening. Women were to avoid becoming pregnant, and must have agreed to refrain from sexual activity or to use reliable contraceptive methods for 30 days before and 30 days after administration of ^{18}F-AV-45 for injection. In order to participate in this study, sexually active females must have been either: 2 or more years postmenopausal or surgically sterilized, or must have been using an acceptable form of contraception (oral contraceptives for at least 3 months or an intrauterine device for at least 2 months before the start of the screening visit, or various barrier methods, eg, diaphragm or combination condom and spermicide).
15. Subjects who, in the opinion of the investigator, were otherwise unsuitable for a study of this type.
16. Subjects with a history of relevant severe drug allergy or hypersensitivity.
17. Subjects who had received an investigational medication within the last 30 days. Additionally, the time between the last dose of the previous investigational medication and enrollment (completion of screening assessments) must have been at least equal to 5 times the terminal half-life of the previous investigational medication. Subjects who had ever participated in an experimental study with an amyloid targeting therapy (eg, immunotherapy, secretase inhibitor)

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could not have been enrolled unless it could be demonstrated that the subject received only placebo in the course of the study;

18. Subjects with current clinically significant medical comorbidities, as indicated by history, physical exam, ECG (including but not limited to QTc >450 ms) or laboratory evaluations, that might have posed a potential safety risk, interfered with the absorption or metabolism of the study drug, or limited interpretation of the study results. These included but were not limited to clinically significant hepatic, renal, pulmonary, metabolic or endocrine disease, cancer, human immunodeficiency virus infection and AIDS;
19. Subjects who received a radiopharmaceutical for imaging or therapy within the past 7 days before the imaging visit for this study.

Study Design:

This study was designed to expand the database of ^{18}F-AV-45 safety and amyloid binding measured by PET imaging in cognitively normal subjects, subjects with AD, and subjects with MCI, and to evaluate the relation between age and apolipoprotein E (ApoE) genotype with amyloid binding in these populations. Approximately 180 subjects were planned to be enrolled. Eighty of the subjects enrolled were to be cognitively normal subjects, distributed roughly equally across age deciles (50-59, 60-69, 70-79 and ≥80 years). Additionally, 40 subjects with AD and 60 subjects with MCI were to be enrolled.

Screening assessments took place over several days and included the informed consent process, collection of demographic information, cognitive testing, safety assessments, and an MRI scan. Screening cognitive tests/psychometric battery included CDR, MMSE, Alzheimer's Disease Assessment Scale (ADAS; only the 11-item cognitive subscale was used in this study), Wechsler Logical Memory I and II Story A (immediate and delayed paragraph recall), Digit-Symbol Substitution, Category Verbal Fluency (animals and vegetables), and ADCS ADL Scale. Additionally, the Geriatric Depression Scale (GDS) was assessed at screening.

Subjects who qualified for the study returned to the clinic at a later date and had a catheter(s) placed for IV administration of ^{18}F-AV-45 for injection. Subjects received a single IV bolus injection of ^{18}F-AV-45, followed by brain PET imaging of 10-minutes duration approximately 50 minutes after dose injection. Vital signs, ECG, and blood and urine samples for clinical laboratory tests were obtained before and immediately after the administration of ^{18}F-AV-45 and at the completion of the imaging visit. Adverse events (AEs) were continuously monitored during the imaging visit. Subjects who experienced any AE were not to be discharged until the event had resolved or stabilized. A follow-up phone call to the subject (or the caregiver as applicable) was to be conducted approximately 7 (±1) days after the imaging visit to confirm subject well-being and to collect information about any new AEs.

Assessments and Endpoints:

Screening: Day 0

Screening may have taken place over several days. However, with the exception of the MRI (below), all screening assessments were to be performed within 30 days before the imaging visit. Screening assessments included:

- Informed consent.
- Demographics (age, gender, education, history of alcohol and drug use, smoking).
- Medical history, physical and neurological exam, concomitant medications.
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of

relevant neurological disease).

- Cognitive testing (CDR, MMSE, ADAS [11-item cognitive subscale], Wechsler Logical Memory I and II Story A (immediate and delayed paragraph recall), Digit-Symbol Substitution, Category Verbal Fluency [animals and vegetables], and the ADCS ADL Scale).
- GDS.
- Safety (vital signs, ECGs, clinical laboratory tests).
- Serum β-hCG level (women of child-bearing potential).
- MRI:
  - If an MRI of the brain was performed within the 6 months before screening and results were available for possible use in normalizing regions of interest from the PET scan, the MRI did not need to be repeated.
- Height and weight measurement.
- ApoE genotyping (optional).
- AE assessment.
- A physician saw the subject during the screening visit.

Imaging: Day 1

The following assessments were performed for all subjects:

- Females of childbearing potential had a urine pregnancy dipstick test before injection (the result must have been negative for the subject to be administered ^{18}F-AV-45).
- Following administration of 370 megabecquerel (10 mCi) of ^{18}F-AV-45 for injection, subjects had continuous PET brain imaging for a period of 10 minutes that began approximately 50 minutes after injection. The images were immediately reconstructed and if motion was detected, the scan was repeated for another 10 minutes.
- Vital signs and a resting ECG were taken with the subjects in a supine position immediately (within 5 minutes) before ^{18}F-AV-45 administration, immediately after ^{18}F-AV-45 administration (approximately 0-1 minute), and again at the end of the study visit before discharge (approximately 70 minutes after ^{18}F-AV-45 administration).
- Blood and urine samples were collected for clinical laboratory tests before administration of ^{18}F-AV-45 and again at the end of the imaging visit before discharge (approximately 70 minutes after ^{18}F-AV-45 administration).
- Subjects were continuously observed for signs of AEs or serious adverse events.
- The injection site was observed for excessive inflammation in or damage to the tissue surrounding where the dose was injected.
- A physician saw the subject before discharge.

Follow-Up: Day 7 (±1)

- Subjects (or their caregivers if applicable) were contacted by phone approximately 7 (±1) business days after they were injected with the investigational agent to confirm their well-being and to query

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them about any new AEs.

Evaluation of Imaging:

The PET images were evaluated qualitatively (blinded readers), semi-quantitatively (blinded readers), and quantitatively (computerized analysis).

Semi-Quantitative and Qualitative Evaluations of Brain PET Images

For semi-quantitative and qualitative evaluations (visual reads), the images were visually examined by 3 readers who were blinded to all clinical information. For the semi-quantitative evaluation, each reader rated the amyloid burden level on a scale from 0 to 4, and the median score of the 3 readers was the primary efficacy endpoint. For the qualitative evaluation, the readers classified images as either positive for amyloid-beta (Aβ+, AD-like) or negative for amyloid-beta (Aβ-, not AD-like). The majority read was the primary efficacy endpoint for the qualitative evaluation. If the image was only read by 2 readers and they differed on their classification, the majority read was classified as Aβ+.

Quantitative Evaluation of Brain PET Images

For the quantitative evaluation (computerized analysis), tracer uptake levels were measured for the following 6 target cortical brain regions: frontal cortex, temporal cortex, precuneus, parietal cortex, anterior cingulate, and posterior cingulate. The cerebellum was measured for use as a reference region. The SUVR was calculated for each cortical target region relative to the cerebellum. The primary efficacy endpoint for quantitative evaluation of each subject was the mean of the SUVRs for the 6 cortical target regions.

Statistical Methods:

Frequency distributions and summary statistics for demographic and baseline characteristics were summarized by clinical diagnostic group for all subjects in the safety population.

For the quantitative evaluation, the mean cortical SUVR (the average of 6 cortical target regions normalized to cerebellum) were summarized by clinical diagnostic group. Analysis of variance values including contrasts were used to compare the mean SUVR between clinical diagnostic groups, and the 95% confidence intervals about the means were included. The cortical SUVR was also summarized and/or analyzed in relation to age, ApoE genotype, and performance on cognitive tests. A multivariate/stepwise analysis was used to analyze the association of results on various cognitive tests with cortical SUVR by clinical diagnostic group, controlling for age, ApoE genotype, and education.

The qualitative classification of the image was summarized by age and by ApoE genotype, and performance on cognitive tests was evaluated as a function of qualitative classification. A multiple regression model was used to analyze the association of each cognitive test with age, education, ApoE4 gene presence (yes/no), and qualitative image classification (Aß+ or Aß-) as possible explanatory variables. The frequency distribution of the qualitative classification of the image (Aß+ or Aß-) was summarized in a table by the median semi-quantitative rating of the image (0-4). The Cochran-Mantel-Haenszel test was used to test the association of amyloid burden rating and qualitative classification. The correlations between the median semi-quantitative amyloid burden rating and scores on the cognitive tests were also derived using Spearman's rank correlation.

Safety variables included extent of exposure, treatment-emergent adverse events (TEAEs), clinical laboratory values, vital signs, and ECGs. Treatment-emergent AEs were undesirable experiences, signs, or symptoms that began or worsened in intensity or frequency at the time of or after the administration of study drug. The numbers and percentages of subjects who experienced TEAEs were presented by clinical

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diagnostic group and overall, and were summarized by relationship to study drug and by intensity/severity. Clinical laboratory values were summarized by clinical diagnostic group for each time point and in shift tables. Vital sign measurements and ECG results were summarized along with changes from baseline values. Tables and listings of all subjects with possible postbaseline clinically significant clinical laboratory values, vital sign measurements, and ECG results were created.

Results:

Subjects/Disposition

One hundred eighty-four subjects were enrolled in the study and treated with ^{18}F-AV-45 (45 subjects with AD, 60 subjects with MCI, and 79 cognitively normal subjects). All enrolled subjects were included in the safety population. A single subject (subject 422-102) received ^{18}F-AV-45 and completed the safety assessments (and thereby completed the study) but due to technical difficulties with the scanner was not imaged and is therefore not included in the efficacy population. Additionally, a single subject (subject 131-102) completed the imaging portion of the study (and is therefore included in the efficacy population) but was subsequently lost to follow-up and discontinued from the study. All other subjects completed the study.

Efficacy Results

- ^{18}F-AV-45 PET image assessments: The semi-quantitative median amyloid burden rating was highly correlated with the quantitative mean cortical SUVR (R=0.808, $P<0.0001$), and there was excellent agreement between the qualitative and semi-quantitative visual reads (100% agreement) and between mean cortical SUVR and qualitative visual reads (91% agreement).
- Clinical diagnostic group: The ^{18}F-AV-45 PET cortical brain signal was highest in subjects with a clinical diagnosis of AD, lowest in cognitively normal subjects, and intermediate in subjects with MCI. All differences between clinical diagnostic groups were statistically significant regardless of whether ^{18}F-AV-45 PET signal was measured quantitatively using SUVR, semi-quantitatively using blinded reader median amyloid burden ratings, or qualitatively using blinded reader classifications of Aβ+ or Aβ-. Results show 75.6% of subjects with AD, 38.3% of subjects with MCI, and 14.1% of cognitively normal subjects were rated as Aβ+. Subjects with clinically diagnosed probable AD were rated as negative for amyloid by qualitative rating of the ^{18}F-AV-45 PET scan in 24.4% of cases. This closely matches the expected prevalence of amyloid-negative individuals in a clinically diagnosed AD population, based on literature reports of the false-positive rate for the clinical diagnosis of AD versus autopsy. Similarly, the observation that 38.3% of subjects with MCI were rated as Aβ+ by the ^{18}F-AV-45 PET scan is consistent with the autopsy literature that shows 33% to 62% of subjects with MCI have amyloid pathology at postmortem examination. Cognitively normal subjects were rated as Aβ+ in 14.1% of cases. The prevalence of amyloid pathology detected at autopsy in cognitively normal individuals varies highly with the age of the subjects studied. Given the age range of the cognitively normal subjects in the present study, the prevalence of amyloid pathology is consistent with the prevalence that would be expected from literature reports.
- Age: In cognitively normal subjects, rates of Aβ positivity increased with age: 5.3%, 10.5%, 15.0%, and 25.0% of cognitively normal subjects aged 50 to 59, 60 to 69, 70 to 79, and 80 years or more, respectively, were rated as Aβ+. These rates of amyloid positivity closely match the prevalence of pathological amyloid detection reported in autopsy studies of cognitively normal elderly subjects.
- ApoE genotype: Subjects in the ApoE2 group had statistically significantly lower mean cortical SUVRs than subjects in the ApoE4 group, regardless of diagnostic category, and no subjects in

the ApoE2 group were rated as Aβ+, regardless of diagnostic category. Subjects in the ApoE3 group had statistically significantly lower mean cortical SUVRs than subjects in the ApoE4 group for subjects with AD and MCI. Additionally, the ApoE4 group had a higher proportion of subjects rated Aβ+ than the ApoE3 group, and this difference was especially large in subjects with AD and MCI. These results are consistent with postmortem studies of subjects with and without dementia, which show that the ε4 allele is a significant risk factor for amyloid burden, that cognitively normal subjects carrying an ε4 allele are more likely to have significant levels of amyloid at autopsy, and that subjects with an ε2 allele have low to no plaque levels, regardless of whether they have dementia.

- Cognitive testing: Across all subjects, subjects with high ^{18}F-AV-45 PET signal performed worse than subjects with low ^{18}F-AV-45 PET signal on all cognitive tests except the GDS, regardless of whether ^{18}F-AV-45 PET signal was measured quantitatively, semi-quantitatively, or qualitatively. For cognitively normal subjects, a higher ^{18}F-AV-45 PET signal was associated with worse performance on a number of cognitive tests, including Wechsler Logical Memory I Story A (immediate paragraph recall) and II Story A (delayed paragraph recall), Digit-Symbol Substitution, ADCS ADL Scale, and the 11-item ADAS cognitive subscale. These findings suggest an association between amyloid burden, as measured by ^{18}F-AV-45 PET signal, and subclinical levels of decreased cognitive performance.
- Multivariate/stepwise analysis: Within cognitively normal subjects, high ^{18}F-AV-45 PET signal was associated with poorer performance on the Wechsler Logical Memory I Story A (immediate paragraph recall) and II Story A (delayed paragraph recall), on the ADCS ADL Scale, and on the 11-item ADAS cognitive subscale. The presence of significant amyloid burden as measured by quantitative and qualitative ratings of ^{18}F-AV-45 was a better predictor of cognitive performance than any other variable for cognitively normal subjects, including age and ApoE genotype, which was not a statistically significant predictor of scores on any of the cognitive tests when either SUVR or the qualitative rating of amyloid burden was included in the model.

Safety Results

- Twenty TEAEs were experienced by 17 subjects (9.2%) in the safety population. The majority of the TEAEs were mild and were considered to have a remote (unlikely) relationship to study drug.
- One SAE of upper limb fracture, which resulted from a trip-and-fall injury, was experienced in this study. This SAE was moderate in severity and was considered to have a remote (unlikely) relationship to study drug. No deaths occurred in this study, and no AEs led to study discontinuation.
- Although statistically significant mean changes in various hematology and serum chemistry parameter values were observed in subjects within all clinical diagnostic groups, these changes were small and not considered clinically meaningful. There was no obvious pattern of shifts in hematology or in serum chemistry parameters following administration of ^{18}F-AV-45. The majority of potentially clinically significant postbaseline hematology and serum chemistry values were observed in subjects who had potentially clinically significant abnormal values before dosing on the imaging day. One incident of increased white blood cell count (before dosing: $9.88 \times 10^3/\mu L$; after dosing: $11.21 \times 10^3/\mu L$) in a cognitively normal subject was reported as a TEAE by the investigator.
- A few statistically significant mean changes were observed in various vital sign measurements and ECG parameters; however, these changes were not considered clinically meaningful. Eighteen subjects had increases from Baseline in systolic blood pressure of greater than 20 mmHg; however, only one event of increased blood pressure (before dosing: 143/58 mmHg; immediately after dosing: 144/58 mmHg; 70 minutes after dosing: 151/66 mmHg) was reported

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals, Inc.	^{18}F-AV-45 for Injection (florbetapir F 18)	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)
as a TEAE by the investigator. No other potentially clinically significant vital sign measures or ECG findings were reported as TEAEs.		
Conclusions: ^{18}F-AV-45 is being developed for use as a PET imaging biomarker of amyloid-beta aggregates in the brain. The results of the present study have shown that an IV injection of ^{18}F-AV-45 is safe and well tolerated and provide supportive evidence of effectiveness of ^{18}F-AV-45 PET for the proposed indication of imaging β-amyloid aggregates in the brain. The ^{18}F-AV-45 PET signal varied as a function of factors known to be related to levels of brain amyloid pathology (clinical diagnosis, age, and ApoE genotype). In addition, this study showed that a high ^{18}F-AV-45 PET cortical brain signal correlated with poorer cognitive performance in cognitively normal elderly control subjects, suggesting that excess accumulation of Aβ may be pathological even in apparently cognitively normal subjects.		
Date of Report: 30 July 2010		

Reviewer's comments:
The A05 study is acceptable from clinical pharmacology perspectives.
However, please note following interaction with the sponsor.
The sponsor decided later on during the development plan that instead of SUVR, a binary read (beta amyloid positive or beta amyloid negative image) would be used clinically. A "beta amyloid positive image" was defined as an image where SUVR would be greater than 1.1. The results of the Study A01 had shown SUVR of 1.24 for cognitively healthy controls. This raised serious concern as PET images for most (12 out of 15) cognitively normal subjects would be read as amyloid positive scan.

Following information request letter was sent to sponsor on November 30, 2010 by clinical pharmacology team:
"….the data from Study A01 and A05 employed healthy volunteers with the age over 50 years. These studies show high numbers of "false positive" for healthy volunteers >50 years of age (MMSE >29) based on SUVR >1.1 as beta amyloid positive image using a visual binary read as proposed by Company. In Study A01, it appeared that 80 % of the healthy volunteers (i.e., 12 out of 15 healthy volunteers) have substantial levels of Beta amyloid showed by PET image (Please refer to Figures 14.4.1.7 and Figure 14.5.1.5 for Study A01). Similarly, in Study A05, it appears that 22.8 % (i.e., 18 out of 79 healthy volunteers) of PET reads (based on visual binary reads) would be assessed as "positive". The % of false positive read for Study A05 appears much better than Study A01.

Please explain how nuclear medicine physician would accurately identify healthy volunteers based on florbetapir-PET scan with the high number of false positive image in healthy volunteers (i.e., 22.8 – 80 %). Also, please explain the discrepancy in the results of two trials (A01 and A05)".

The sponsor responded, "The SUVR values in Study A01were calculated using different brain regions than the SUVR values in subsequent studies and a cut point of SUVR >

1.10 cannot be used for A01. The most important difference was that the reference region for Study A01 was cerebellar gray matter, whereas the whole cerebellum was used in later studies. (Cerebellar gray matter has lower activity than the cerebellum as a whole and using the cerebellar gray matter made the Study A01 values higher, on average, than those from the later studies.) This change to using the whole cerebellum was made in the subsequent studies to improve the reliability of calculation. As a consequence, the cut point of 1.10, proposed for later studies does not apply to the original A01 data.

We note, however, that the A01 images were reanalyzed using the whole cerebellum reference region in Study A06. Study A06 Listing 14.8 lists the revised SUVR values for all subjects. Instead of 12 subjects, only 3 of 15 HC from study A01 had SUVR > 1.10. These were 012-003 (1.27, age 84), 012-006 (1.42, Age 84) and 012-020 (1.18, Age 80). These subjects were also read visually positive. This rate of positive HC (20%) is consistent with the rate in our other studies, including A05."

Comparison of PET images acquired at 30 min and 50 min post injection of ^{18}F-AV-45 in Healthy Volunteers and Alzheimer's disease Patients

Study Design:	This study uses blinded reads from three independent readers of florbetapir-PET images to evaluate the level of agreement between readings at 30-40 minutes and 50-60 minutes post-dose. The study uses images acquired from two previous studies of florbetapir-PET imaging (^{18}F-AV-45-A01 and ^{18}F-AV-45-A03).
Sponsor:	Avid Radiopharmaceuticals, Inc
	Sponsor's Responsible Medical Officer: Daniel M. Skovronsky, MD, PhD
	Sponsor's Contact Person: Michael J. Pontecorvo, PhD Telephone: 215-298-0700 Fax: 413-826-0416
Report Date	30 July 2010

This study was performed in compliance with the principles of good clinical practice (GCP). The information contained in this Clinical Study Report is CONFIDENTIAL and the information contained within it may not be reproduced or otherwise disseminated without the approval of Avid Radiopharmaceuticals.

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals, Inc.	^{18}F-AV-45 for Injection	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

Title of Study: Comparison of PET images acquired at 30 min and 50 min post injection of ^{18}F-AV-45 in healthy volunteers and Alzheimer's disease patients.

Test Product: ^{18}F-AV-45

Dose: 10 mCi (370 MBq) and 3mCi (111MBq)

Route of Administration: Intravenous (IV) bolus

Study Phase: N/A

Study Centers:

This report describes the results of an independent, randomized blinded read of images collected in two previous studies, A01 and A03, at 5 imaging centers.

The ^{18}F-AV-45-01 (A01) study was conducted at 3 study centers: The Johns Hopkins University (site 012, Dr. Wong), The Memory Enhancement Center (site 023, Dr. Ross), and Community Health Research (site 026, Dr. Edell).

The ^{18}F-AV-45-A03 (A03) study was conducted at 3 study centers: Clinical Research Institute (Site 124, Howard A Hassman, MD), Community Health Research (Site 226, Stephen Edell, DO), and Premiere Research Institute (Site 322, Carl Sadowsky, MD).

Objectives:

The objectives of this blinded evaluation of 30-40 minute and 50-60 minute (standard) post-injection florbetapir-PET images were:

- To test whether a qualitative read of a PET scan collected at 30-40 minutes post-injection (the 30 minute image) provides equivalent results to a qualitative read of a PET scan collected at 50-60 minutes post-injection (the 50 minute image).
- To compare the results of a semi-quantitative read of the 30 minute image to a semi-quantitative read of the 50 minute image.
- To measure and summarize inter-reader reliability (intra-class correlation coefficients) for qualitative and semi-quantitative assessments of the 30 minute images and 50 minute images.
- To measure and summarize SUVRs obtained from the 30 minute images and 50 minute images.

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Number of Subjects Used for this analysis:

Two earlier studies, ^{18}F-AV-45-A01 (A01) and ^{18}F-AV-45-A03 (A03) employed continuous dynamic PET imaging over time periods ranging from 0 to 90 minutes post-injection. Data from all subjects with technically valid images collected from 30-40 minutes post-injection and 50-60 minutes post-injection of florbetapir F18 were used in the independent blinded read analysis.

In total, the randomized, independent blinded reading of 30 and 50 minute florbetapir-PET images carried out in this study was conducted on data from 41 subjects (18 subjects having a clinical diagnosis of AD and 23 cognitively-normal subjects).

Eligibility:

The CSRs for studies A01 and A03 contain the eligibility and exclusion criteria for each study respectively. To briefly summarize the subject population, in study A01 the healthy volunteers were intended to be roughly comparable in age to the AD patients, i.e. >50 years of age. In study A03, an attempt was made to recruit relatively amyloid free volunteers, and thus the healthy volunteers were between 35 and 55 years of age. For the purposes of the present analysis, cognitively healthy volunteers will be classified as young healthy volunteers (YHV) if they are less than 50 years of age, and as cognitively-healthy volunteers (HV) if their age is >50 (i.e. roughly comparable in age to AD subjects in the A01 and A03 studies). Subjects with AD met established NINCDS criteria for probable AD and had a MMSE score at screening between 10 and 24, while HV subjects were cognitively normal on the screening psychometric test battery and had a MMSE score ≥29.

Study Design:

For this study, images from a total of 22 subjects from trial A01 and 19 subjects from trial A03 were used. For each subject, 30 minute images and 50 minute images were presented in random order (i.e. interspersed with scans from other subjects at both time points) to three independent readers who were blinded to clinical information and the time point for each image. The readers evaluated the PET images both qualitatively and semi-quantitatively. A quantitative analysis of images acquired at 30-40 minutes and 50-60 minutes was also completed using a standardized, semi-automated quantitative analysis which provided a cortical to cerebellum standardized uptake value ratio (SUVR) for both the 30 minute and 50 minute florbetapir-PET scans.

Assessments:

Detailed descriptions of the assessments used in subject screening and safety monitoring for studies A01 and A03 are provided in their respective study reports. A brief summary of imaging procedures is provided below for these two studies.

Image acquisition

On imaging day, subjects were administered with either 3mCi (5 AD and 4 HV in study A03) or

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10mCi of florbetapir F 18 (3 AD and 7 HV from study A03 and 10 AD and 12 HV in study A01) after which brain PET imaging commenced continuously for up to 90 minutes.

Preparation of Imaging Data for evaluation:

Florbetapir-PET images which included data from 10 minute scans acquired over a period 30-40 minutes post-injection and 50-60 minutes post-injection were generated for each subject. These images were de-indentified and blindly evaluated per the Independent Review Charter and Reader Training Manual, respectively. For the independent blinded visual read assessment, a total of 82 florbetapir PET images were reviewed from the 41 available subjects.

Evaluation of Imaging:

Three (3) readers (radiologist or nuclear medicine specialist), blinded to subject identification, subject diagnosis, subject demographics and PET scan time points randomly and independently read the PET scans at the central imaging core lab. The three readers for this study had not participated in the enrollment of subjects or in any previous reviews of these images. For this study, the blinded readers determined whether the subjects' PET scans were Aß positive (AD-like) or Aß negative (control-like) as well as provided an overall semi-quantitative global score of cortical β-amyloid levels from 0-4 in accordance with the Independent Review Charter for this study. All reader data was collected on CRFs.

Additionally, PET scan images were processed in accordance with standard operating procedures to provide the standardized uptake value ratio (SUVR) for the cortical average (calculated as the average of the following six regions: frontal, temporal, parietal, precuneus, anterior cingulate, and posterior cingulate relative to the cerebellum). For images from study A03, the SUVR values as reported in the original study report were used for this pooled analysis. However, because A01 was the first study conducted with florbetapir F 18, the original analysis methods were exploratory and method improvements were made over the course of successive studies. Thus, following study A01, the placement of brain regions (defined as Volumes of Interest-VOI) were modified and improved for quantitation of florbetapir uptake in certain regions. In order to directly compare the SUVR data from A01 images with A03 images in a pooled analysis, the improved methods/VOI as used in study A03 were applied to the images from study A01. Thus, the final SUVR analysis for A01 used in this report were derived and calculated consistently with all other Phase II and III studies (A03, A04, A05 and A07).

Statistical Methods:

Subjects were assigned to one of the following diagnostic subgroups based on clinical evaluation: Alzheimer's Disease (AD), Cognitively Healthy Volunteer (HV, also referred to as Healthy Controls (HC)) and Young Healthy Volunteer (YHV, also referred to as Young Healthy Controls (YHC)). YHVs are defined as a subset of HVs that are less than 50 years of age.

The agreement between the 30 minute and 50 minute image time points was reported and summarized for the qualitative and semi-quantitative evaluations. A kappa statistic was used to summarize the chance corrected agreement in the qualitative scores and the semi-quantitative

scores. In addition, the correlation between 30 minute and 50 minute image scores was determined and a scatter plot was created. Inter-reader reliability for each image time point was computed using an intra-class correlation coefficient (i.e. the consistency of agreement among readers was calculated at each time point, respectively). The reliability of readers (as the Intraclass Correlation Coefficient) between the two image time points are also summarized and compared.

For the SUVR analysis, the correlation between the two image time points was computed using a Pearson correlation. A scatter plot of SUVR for the two time points was provided. Additionally, a Bland Altman plot was provided for the SUVR difference.

Primary Analysis: Agreement between qualitative blinded ratings of 30 and 50 minute images

The level of agreement between the two time points was tested using agreement statistics. Using the 50 minute image read majority as the reference, the hypothesis tested was that the 30 minute image read majority score will have an observed agreement with the reference of at least 0.85. Agreement between the two time points was also computed using a kappa statistic. Inter-reader reliability at each time point was computed using an intra-class correlation coefficient.

Results:

Using the majority qualitative read of the 3 readers, there was 100% agreement between the 30 minute image evaluation and the 50 minute image evaluation (100% agreement within each clinical diagnostic subgroup). Similarly, agreement measured using the kappa statistic was 100% for each diagnostic subgroup.

Overall inter-reader reliability (i.e. intraclass correlation coefficient) using the qualitative reads was observed to be 0.816 at both 30 minute and 50 minute post-injection time points.

Using the median semi-quantitative read of the 3 readers, agreement between the 30 minute images and 50 minute images measured using the Cohen-Fleisser (quadratic) kappa statistic was 0.946 for the overall efficacy population. Correlation between the 30 minutes images and 50 minutes images semi-quantitative median reads was observed to be 0.948 which is highly statistically significant (1-sided p-value <0.0001).

Overall inter-reader reliability (ICC) using the semi-quantitative reads was observed to be 0.812 at both the 30 minute and 50 minute post-injection time points.

The average cortical to cerebellar SUVR values in AD patients, but not the HV subjects, show continual substantial increases from time zero through 30 minutes post-administration, with only small changes thereafter up to 90 minutes post-injection. The time activity curve for YHV was similar to that for HV. The ratio of AD to HV cortical average SUVRs appeared relatively constant between 30 and 90 minutes, and the effect size using Cohen's d were comparable at 30

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and 50 minutes (3.25 and 2.84, respectively). Similar results were obtained comparing AD subjects to YHV at 30 and 50 minutes. The correlation between the two time points, across all subjects analyzed, was 0.988 and was highly statistically significant (1-sided p-value <0.0001).

Conclusions:

The results of this study, demonstrated that there is no significant difference between florbetapir-PET scans acquired at 30 and 50 minutes post-injection with respect to the blinded reader visual assessment or the SUVR quantitative analysis.

Date of Report: 30 July 2010

Reviewer's comments:

The study A06 is acceptable from clinical pharmacology perspectives. This reviewer agrees with the sponsor's conclusion that the imaging time can be in between 30 -50 min after the administration of flobetapir F-18.

Reference ID: 2904801

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

Protocol Number:	^{18}F-AV-45-A07
Phase:	III
Investigational Product:	Florbetapir F 18 (^{18}F-AV-45)
Indication Studied:	PET imaging of β-amyloid pathology
Study Design:	A blinded study designed to test the correlation and agreement between measurements of β-amyloid by florbetapir F 18 positron emission tomography imaging and levels of β-amyloid determined by histopathological analysis at autopsy
First Subject Enrolled:	24 February 2009
Last Subject Completed:	19 March 2010
Sponsor:	Avid Radiopharmaceuticals, Inc.
	Sponsor's Responsible Medical Officer: Christopher M Clark, MD
	Sponsor's Contact Person: Michael J. Pontecorvo, PhD Telephone: 215-966-6221 Fax: 413-826-0416
Report Date	Final 24 August 2010

This study was performed in compliance with the principles of good clinical practice. The information contained in this Clinical Study Report is CONFIDENTIAL and the information contained within it may not be reproduced or otherwise disseminated without the approval of Avid Radiopharmaceuticals.

Sponsor:	**Name of Compound:**	**Active Ingredient(s):**
Avid Radiopharmaceuticals	Florbetapir F 18 Injection	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

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

Test Product: Florbetapir F 18 (^{18}F-AV-45)

Doses: 370 Megabecquerel (MBq) (10 milliCurie [mCi])

Route of Administration: Intravenous (IV) bolus

Study Phase: III

Study Centers: The study was conducted at 34 study centers in the United States, 25 of which enrolled at least 1 subject.

Objectives: This study was designed to test the relationship between measurements of amyloid burden using florbetapir F 18 positron emission tomography (florbetapir-PET) imaging and true levels of amyloid burden determined at autopsy. In addition, the study tested the specificity of florbetapir-PET to accurately identify the absence of amyloid pathology. The study tested the following two hypotheses:

Primary hypothesis #1: Correlation analysis

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, $p \leq 0.05$, $\rho>0$, was used to assess a significant correlation.

Primary hypothesis #2: Specificity analysis

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, which yields 95% CI bounds of 80% to 98% for n=40).

Number of subjects (Enrolled): A total of 226 subjects were enrolled in the study, 152 subjects in the autopsy cohort and 74 young healthy volunteer subjects in the specificity cohort.

Main Eligibility Criteria:

Autopsy cohort: Male or female subjects, ≥18 years of age, who had a projected life expectancy of ≤6 months (or other end-of-life subjects who were already enrolled in longitudinal studies of aging) and could tolerate a 10-minute PET scan were eligible to enroll in the autopsy cohort. An effort was made to enroll subjects with various levels of

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cognitive status, ranging from cognitively normal through dementia. It was expected that amyloid burden in this population would range from very low (normal aging) through moderate (e.g., cognitively normal subjects with asymptomatic amyloid deposits or mild cognitive impairment [MCI] and some AD subjects with intermediate levels of amyloid deposits) to very high (some AD subjects).

Specificity Cohort: Cognitively and neurologically healthy male and female subjects, 18 to 40 years of age, who had no known risk factors for Alzheimer's disease (AD), including genetic risk factors for AD, such as apolipoprotein (Apo) E ε4, performed in an age-appropriate normal range on the Wechsler Logical Memory I & II, story A, and could tolerate a 10-minute PET scan were eligible to enroll in the specificity (young control) cohort.

Subjects with brain tumors or other major focal brain abnormalities, and subjects being aggressively treated with life-sustaining measures were ineligible for enrollment. In addition, subjects that had ever participated in an experimental study with an amyloid targeting agent or had recent radiopharmaceutical exposure and females of childbearing potential who were pregnant or not using adequate contraception were also ineligible for enrollment in either cohort.

Study Design: This study tested the relationship between measurements of β-amyloid using florbetapir-PET imaging and levels of β-amyloid determined by histopathological analysis at autopsy. A total of 226 subjects were enrolled in the study. For the autopsy cohort, 152 subjects were enrolled from various end-of-life (e.g., hospice/hospital/nursing home) and late-life (longitudinal studies of aging) populations to yield 35 autopsies within 1 year following the PET imaging procedure.

The first 6 subjects to come to autopsy were considered front runners, and an interim analysis was completed on data from these subjects in order to finalize the study methods. No significant changes in the clinical study protocol, the PET image Independent Review Charter, or the Neuropathology Analysis Protocol were made following the front runner review. The front-runner analysis confirmed that an autopsy study population of 29 was sufficient to test the primary correlation hypothesis in the main phase of the trial.

Three independent imaging physicians evaluated 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.

An additional cohort of young (age < 40), cognitively and neurologically healthy individuals was enrolled for specificity analysis of florbetapir-PET. The control scans were randomly mixed with scans rated positive (median rating of 2, 3 or 4) from the

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Avid Radiopharmaceuticals	Florbetapir F 18 Injection	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

autopsy cohort for the blinded reading by three additional independent imaging physicians for the specificity evaluation.

Evaluation of Imaging: Florbetapir-PET images were evaluated qualitatively (specificity cohort blinded readers), semi-quantitatively (autopsy cohort blinded readers), and quantitatively (semi-automated computerized analysis). All image evaluations and analyses were completed at the Imaging Core Lab.

Semi-quantitative and Qualitative Evaluations of Brain PET Images: For semi-quantitative (autopsy cohort read) and qualitative (specificity cohort read) evaluations, the images were visually examined by two separate groups of 3 readers who were blinded to all clinical information. For the autopsy cohort, a visual semi-quantitative rating assessment was performed by three independent readers. Each autopsy-cohort reader rated the degree of florbetapir retention in the grey matter on a scale from 0 (no amyloid) to 4 (high levels of β-amyloid deposition), and the median score of the 3 readers was the primary efficacy endpoint.

For the specificity cohort (qualitative) blinded read, a new group of three readers classified images as either positive for β-amyloid (Aβ+, AD-like) or negative (Aβ-, not AD-like). In order to minimize bias for the qualitative specificity image read, the specificity cohort images were randomly mixed with 40 positive scans selected from those rated positive (2, 3, or 4) in the autopsy cohort blinded read. The majority qualitative read result of the blinded readers was the primary efficacy endpoint for the specificity evaluation.

Quantitative Evaluation of Brain PET Images: For the quantitative evaluation (computerized analysis), the ratio of cortical to cerebellar signal (SUVR) was performed for florbetapir-PET images for all subjects. Standardized uptake values ratios (SUVRs) were calculated for the following 6 target cortical brain regions: frontal cortex, temporal cortex, 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.

Autopsy Procedures and Analysis: For the quantitative analysis of β-amyloid burden, as determined by IHC, tissue sections were prepared from each of the six primary analysis regions designated for evaluation as well as the cerebellum. The histology process was defined in the Neuropathology Analysis Protocol. Briefly, tissue sections from the regions of interest were stained with 4G8 anti-amyloid antibody and percent area occupied by β-amyloid was measured. Slide level results were averaged to yield regional and global assessments. The global cortical amyloid burden measured by IHC was the primary outcome variable.

For the semi-quantitative evaluation of neuritic plaque burden, tissue sections from the

primary analysis regions were stained with a silver stain (modified Bielschowsky) and were read by two readers who were blinded to the clinical history and imaging data. On each tissue sample, the readers independently identified the area of highest plaque counts and an area of plaque counts most representative of the cortical plaque burden and counted the number of neuritic amyloid plaques in a 1 mm^2 gratical. A senior neuropathologist overread all values and corrected any discrepancies. Each reader's regional counts were converted to a semi-quantitative scale using the modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) algorithm described in the table below and averaged across readers and regions to yield regional and global results.

Modified CERAD Scoring with Counts		
Average Counts for a Region	**Regional Semi-quantitative CERAD Score**	
<1	0	(none)
1-5	1	(sparse)
6-19	2	(moderate)
20+	3	(severe)

For all subjects, the senior neuropathologist reviewed a subset of tissue slides and provided a final pathologic diagnosis for AD (using both the CERAD and National Institutes on Aging [NIA]-Reagan Criteria).

Statistical Methods: All correlation analyses were one-sided while all other statistical tests were two-sided with a significance level of α=0.05 and were performed using statistical analysis system (SAS®) version 9.0 or higher. Data were summarized using descriptive statistics.

For the primary efficacy correlation analysis and the secondary efficacy analysis, Spearman's rank order correlation was determined as well as the asymptotic standard error (ASE) and 95% CI using Fisher z-transformation. For the primary efficacy specificity analysis, the number and percent of Aβ- and the 95% CI was determined using the florbetapir F 18 PET scan. Exploratory efficacy analyses were also conducted. All adverse event summaries were prepared using the set of treatment-emergent adverse events only. Treatment-emergent adverse events were summarized by cohort (autopsy, non-autopsy specificity) as well as all subjects (both cohorts). The change from baseline in clinical laboratory values and vital sign measurements were analyzed within treatment group.

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Subjects/Disposition: A total of 226 subjects were enrolled in the study, 152 in the autopsy cohort (56 subjects with AD, 25 subjects with MCI, 21 with other dementing disorders, and 50 cognitively normal subjects) and 74 (all cognitively normal) in the specificity cohort. At the end of the study, 110 subjects in the autopsy cohort were alive and had valid images, and 37 subjects had died. Of the 37 subjects who had died, consent to perform the autopsy for 2 subjects was withdrawn by their families. Thus, there were 35 subjects in the autopsy cohort who completed the trial and had data available for the correlation efficacy analyses. The first six subjects to come to autopsy were used in the front-runner analysis, and the remaining 29 subjects comprised the primary efficacy population for the autopsy cohort. Of the 74 subjects in the specificity cohort, 47 were identified as non-ApoE ε4 carriers and were included in the primary specificity efficacy analyses. All 226 subjects injected with florbetapir F 18 were included in the safety analyses.

Efficacy Results: For all applicable efficacy results, correlations were assessed between key florbetapir-PET measures and key pathologic reference measures using Spearman's rank order correlation, and Spearman's ρ was reported as the correlation coefficient for each test.

- **Primary Correlation Analysis:** A statistically significant Spearman's ρ of 0.78 ($p<0.0001$, 95% CI: 0.58 - 0.89) was observed between the median of the independent reader semi-quantitative visual ratings of amyloid detected on the florbetapir-PET image and the cortical amyloid level as assessed by quantitative IHC (average percent cortical grey matter area of β-amyloid on the IHC slides).
- **Primary Specificity Analysis:** The observed specificity of florbetapir-PET imaging from the independent reader (majority) qualitative visual rating in the specificity cohort was 100% (95% CI: 91% - 100%).
- **Secondary Analyses:** Statistically significant relationships were observed between the 6 regional semi-quantitative visual ratings of amyloid burden on the florbetapir-PET image and the regional cortical amyloid levels as assessed by quantitative IHC. The correlation coefficients between the six analysis regions and regional measures of IHC ranged from 0.68 - 0.77 ($p<0.0001$, 95% CI: 0.42 - 0.88)
- **Exploratory Analyses including front runner subjects (n=35):**
  - 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)
  - The correlation between the semi-quantitative visual rating of amyloid on the florbetapir-PET scans and a numerical representation of the blinded

neuropathologist's diagnosis using the modified CERAD criteria was 0.77 ($p<0.0001$, 95% CI: 0.59 - 0.89).

- The correlation between the semi-quantitative visual rating of amyloid burden of the florbetapir-PET images and the semi-quantitative measure of overall highest neuritic plaque density using modified CERAD scoring was 0.73 ($p<0.0001$, 95% CI: 0.52 - 0.85).
- The correlation between the quantitative SUVR analysis of the florbetapir-PET images and semi-quantitative measure of overall highest neuritic plaque density using modified CERAD scoring was 0.74 ($p<0.0001$, 95% CI: 0.54 - 0.86).
- The correlation between the two principal measurements of pathology (cortical amyloid burden assessed by quantitative IHC and the overall highest plaque density using modified CERAD scoring) was 0.86 ($p<0.0001$, 95% CI: 0.75 - 0.93).
- The correlation between the two principal measurements of PET (semi-quantitative visual rating and quantitative SUVR analysis) was 0.85 ($p<0.0001$, 95% CI: 0.72 - 0.92).

Correlation results did not change significantly whether or not the front-runner subjects were included.

- **Agreement Analyses (autopsy cohort, n=35):** Within the autopsied subjects, 19 subjects met neuropathologic criteria for AD (CERAD and NIA-Reagan). Of these, 18 had florbetapir-PET scans that were interpreted as positive (median read ≥ 2), and all 19 were considered positive by quantitative analysis (cortical average SUVR ≥ 1.10). The other 16 autopsied subjects had low levels of β-amyloid aggregates at autopsy and did not meet pathologic criteria (CERAD or NIA-Reagan) for AD. All 16 had negative florbetapir-PET scans by both visual read and quantitative analysis. Based on the autopsy cohort results the estimated sensitivity of florbetapir PET was 95% by visual read (95% CI: 72% to 98%) and 100% by quantitative analysis (95% CI: 79% to 100%). Specificity was 100% (95% CI: 76% to 100%) by both visual read and quantitative analysis. In the autopsy cohort, visual assessment of florbetapir-PET images agreed with final post-mortem autopsy results in 34/35 cases, yielding an accuracy of 97% (95% CI: 83% to 100%).
- **Clinical Diagnosis Comparison:** On an exploratory basis, clinical diagnosis was compared to final autopsy diagnosis. Of the 23 subjects in the autopsy cohort who had dementia diagnoses in life (AD or other dementias), 3 (13%) had a clinical diagnosis that did not match the final autopsy diagnosis: a single subject

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals	Florbetapir F 18 Injection	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

had a diagnosis of probable AD in life, but was negative for AD at autopsy; and 2 subjects had a 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. The florbetapir-PET scan blinded read result agreed with the autopsy diagnosis in all three of these cases.

Safety Results: One subject in the autopsy cohort experienced a serious adverse event (respiratory failure) during the 48-hour safety monitoring period that resulted in death. The investigator considered the event unrelated to administration of florbetapir F 18. No other serious adverse events were reported during this study.

The most commonly reported treatment-emergent adverse event was headache, which occurred in 5 (2.2%) subjects, including 3 (2.0%) in the autopsy cohort and 2 (2.7%) in the specificity cohort. Fatigue and insomnia were each reported in 2 subjects (1 in each cohort for both events). All other treatment-emergent adverse events occurred in no more than 1 subject, with no apparent pattern that could be attributed to either the cohort or the administration of florbetapir F 18.

Although the paired t-test revealed statistically significant mean changes in various hematology values, chemistry values, urinalysis values, and vital sign measurements in both cohorts, these changes were small and not considered clinically meaningful.

Potentially clinically significant laboratory values were reported in some subjects in this study. These subjects typically had baseline values close to the limits of normal, so that change post-treatment was typically small, of no clinical consequence, and did not result in symptoms or an adverse event.

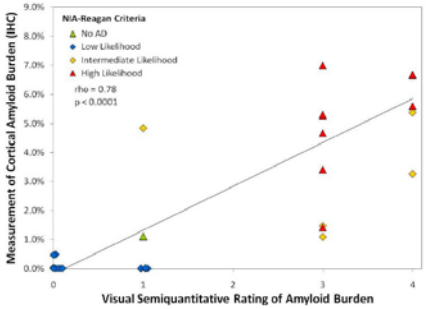
One subject (217-004) had a laboratory value that was reported as a treatment-emergent adverse event. The subject had an abnormal urine color (change in urine color) approximately 28.5 hours after injection of florbetapir F 18 that resolved the next day. The event was considered unrelated to the injection of florbetapir F 18. Two subjects (066-019 and 522-004) had vital sign measurements related to increased blood pressure that were reported as treatment-emergent adverse events. Subject 066-019 experienced an increase in blood pressure (from 120/60 mmHg to 160/100 mmHg) and Subject 522 004 experienced moderate hypertension (increased from 150/90 mmHg to 160/120 mmHg); both events resolved quickly and only one was considered possibly related to the administration of florbetapir F 18.

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals	Florbetapir F 18 Injection	(*E*)-4-(2-(6-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy) ethoxy)pyridin-3-yl)vinyl)-*N*-methylbenzenamine (^{18}F-AV-45)

Conclusions: The results of this study demonstrate that florbetapir-PET accurately detects the presence and density of β-amyloid aggregates. Strong statistically significant positive correlations were observed between florbetapir-PET (both visual blinded reader assessment and computerized SUVR measurement) and histopathologic measurements of β-amyloid. The specificity of the florbetapir-PET scan blinded read was 100% in this study. The study met both of the primary endpoints: 1.) a significant correlation was observed between the visual reader semi-quantitative assessment of florbetapir-PET scans and the amyloid burden measured at autopsy by immunohistochemistry, and 2.) the measured specificity in the specificity cohort was > 90%. In addition, this study demonstrated that the previously defined quantitative SUVR measurement threshold of ≥1.10 for a positive (i.e., abnormal) scan was highly accurate for the detection of pathologically significant β-amyloid levels. Florbetapir F 18 Injection was well tolerated in this study. There was one serious adverse event/death occurring in the autopsy cohort during the safety monitoring period and was considered unrelated to drug treatment. The overall adverse event rate was not higher in the end-of-life autopsy population as compared to the healthy volunteers enrolled in this study. The 35 autopsy cohort subjects enrolled in this study encompassed a broad spectrum of cognitive impairment (from normal cognition to severe dementia) along with the associated broad range of pathology (from none through dense plaques), which demonstrates the wide dynamic range of correlation between florbetapir-PET and histopathological measurements of β-amyloid.

Date of Report: Final 24 August 2010

Reviewer's comment:
The A07 study has been reviewed in detail by reviewing medical officer and statistician. The clinical pharmacology review focused on the correlation of SUVR with the autopsy data, as well as with various stage of neural disease including healthy volunteers.
It appeared that there is statistically significant correlation between SUVR and amount of amyloid plague estimated by autopsy. With this correlation, the SUVR could be used as an important parameter for the non-invasive, quantitative measure of amyloid.



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4.3. Consult review (Including pharmacometric review)
Not applicable. There was no consult review.

4.4. Coversheet and OCP filing review form
Please refer to the DARRTS signed off on 12/21/2010 under NDA 202-008.

Reference ID: 2904801

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

/s/

CHRISTY S JOHN
02/11/2011

YOUNG M CHOI
02/11/2011
I concur.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202008**	**Brand Name**	**F-18 Florbetapir**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	
Medical Division	**DMIP**	**Drug Class**	**Imaging**
OCP Reviewer	**Christy S. John, Ph.D**	**Indication(s)**	**For detection of beta amyloid plaques**
OCP Team Leader	**Young Moon Choi, Ph.D.**	**Dosage Form**	**Clear Injectable Solution**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**10 mCi**
Date of Submission	**September 16, 2010**	**Route of Administration**	**IV**
Estimated Due Date of OCP Review		**Sponsor**	**Avid Radiopharmaceuticals**
Medical Division Due Date		**Priority Classification**	**P**
PDUFA Due Date	**March 17, 2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology	**X**	**1**		
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -		**1**		
Healthy Volunteers-				
single dose:	**X**			
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -		**1**		
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -		**2 (In-Vitro)**		
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

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gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:		**x**		
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**			
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate	X			

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	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___YES_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Christy S. John 10/12/10
Reviewing Clinical Pharmacologist Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

Reference ID: 2881745

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Team Leader/Supervisor	Date
Young Moon Choi, Ph.D.	10/12/10

Reference ID: 2881745

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

/s/

CHRISTY S JOHN
12/21/2010

YOUNG M CHOI
12/21/2010