

Avid Radiopharmaceuticals, Inc.

**FDA Advisory Committee Meeting
October 23, 2008**

^{18}F -AV-45: PET Amyloid Plaque Imaging Agent

**Summary of Development Program
and Proposed Phase III Plan**

Background Package

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1. EXECUTIVE SUMMARY

Development Summary

¹⁸F-AV-45 was selected as the compound with the best properties for imaging amyloid among multiple amyloid ligands from different structural groups tested in comparative trials under exploratory INDs.

More than 200 subjects have been imaged with ¹⁸F-AV-45 under an Avid IND at 20 sites using standardized methods for drug production, imaging, safety monitoring, and data analysis.

Current Status: Late Phase II (anticipated completion 11/08)

Completed Trials

- **Ph I** Brain Imaging
- **Ph I** Safety / Radiation Dosimetry
- **Ph II** Dose Selection
- **Ph II** Test-Retest Reproducibility

Ongoing Trials

- **Ph II** AD, MCI and healthy controls
- **Ph III** Image / Treat / Image
(¹⁸F-AV-45 is used as a biomarker in Eli Lilly's LY450139 γ -secretase inhibitor trial)

Proposed Indication

¹⁸F-AV-45 is indicated for PET imaging of amyloid plaque pathology in the brain to aid in the evaluation of patients with signs or symptoms of cognitive impairment.

Reference Standard

Avid proposes to use post-mortem histopathology as the reference standard in the pivotal Phase III (A07) study.

Clinical Utility

Amyloid plaque pathology is a required feature of AD diagnosis. Patients who are negative for amyloid pathology do not have AD. The presence of amyloid pathology is a supportive feature for diagnosis of probable AD.

Development Plan

Avid seeks initial approval based on an imaging-to-autopsy histopathology correlation study supported by clinical and non-clinical data that establish negative predictive utility (i.e. negative image = negative amyloid pathology = not AD).

Post-Approval Commitments

Large longitudinal studies are needed to establish additional clinical utilities of amyloid imaging, including prognostic applications. From a practical standpoint these studies can only be accomplished over a five to ten year period post-approval. Avid will commit to conduct long-term Phase IIIb, Phase IV and registry studies to establish positive predictive utility and prognostic utility.

¹⁸F-AV-45 is a PET amyloid imaging agent that has been studied in more than 200 subjects in Phase I and Phase II clinical studies. Clinical and non-clinical studies conducted to date indicate that ¹⁸F-AV-45 is well tolerated and has the potential to be effective for in-vivo imaging of amyloid pathology in patients with signs of cognitive impairment.

Avid proposes the following initial indication: ***¹⁸F-AV-45 is indicated for PET imaging of amyloid plaque pathology in the brain to aid in the evaluation of patients with signs or symptoms of cognitive impairment.*** In order to support this indication Avid will conduct studies to demonstrate the following key points: (1) ¹⁸F-AV-45 is a safe and effective marker for determining the presence or absence of amyloid plaque pathology in the brain; (2) A negative ¹⁸F-AV-45 signal in cortical brain regions indicates lack of amyloid plaques and thus is a clinically useful finding to exclude AD as a potential diagnosis.

This plan is consistent with FDA guidance documents that suggest indications for medical imaging drugs may be directed to pathology detection, and also emphasize the need to demonstrate clinical utility (*Guidance for Industry: Developing Medical Imaging Drug and Biological Products, Part 2. Clinical Indications*, June 2004).

The definition of AD includes behavioral signs of dementia and pathological features that are defined in post-mortem histopathological analysis. The presence of amyloid plaques is an absolutely required feature for the definitive diagnosis of AD, as accepted by the American Academy of Neurology, American Psychiatric Association (DSM-IV) and both the CERAD and NIA-Reagan Institute neuropathological criteria. We thus propose to demonstrate the effectiveness of ¹⁸F-AV-45 PET for evaluating amyloid plaque pathology in vivo by comparing imaging results to autopsy-based plaque histopathology (i.e. the truth or gold standard) in terminally ill subjects. The patient sample size of this pivotal autopsy correlation study will be modest (due to practical considerations we anticipate 30 - 50 autopsies), however multiple brain regions will be analyzed for each subject enrolled. We will also supplement the autopsy correlation study with larger controlled studies in well defined populations (such as patients with a clinical diagnosis of AD, patients with other neurodegenerative dementias, and cognitively normal subjects) having high or low probability of amyloid plaque pathology. In these studies we will show that in populations of cognitively impaired patients (and in healthy elderly subjects) ¹⁸F-AV-45 gives the expected prevalence and distribution of signal predicted for an effective amyloid imaging agent. These supportive studies will also provide a large safety database for ¹⁸F-AV-45. Through this combined approach Avid intends to demonstrate that ¹⁸F-AV-45 is safe and effective for imaging amyloid plaques.

The primary clinical utility proposed for ¹⁸F-AV-45 PET at this stage of development is the predictive value of the negative scan. By definition, patients without amyloid plaque cannot have AD. Thus, pre-mortem knowledge of amyloid plaque status would prevent amyloid plaque negative subjects from receiving an incorrect diagnosis of AD, thereby improving the specificity of clinical diagnosis. Correctly eliminating AD from the differential diagnosis of these cognitively-impaired patients is clinically useful for diagnostic, prognostic and therapeutic purposes. Specifically, patients who do not have AD: (1) should undergo further diagnostic testing to elucidate the true cause of their cognitive deficit; (2) have a different prognosis than those with AD; and (3) should receive therapeutic management appropriate for their specific diagnosis. This clinical utility of evaluating amyloid plaque pathology is well supported by the clinical literature. Currently, many patients with signs of dementia are misdiagnosed: 15% - 20% of clinically diagnosed AD patients do not have AD at autopsy and the majority (80% -

100%) of these non-AD patients are amyloid plaque negative (for detailed discussion and references see section 7).

Clinical trials in support of the initial new drug application will include a histopathology correlation trial together with other supportive studies which will enroll both cognitively normal individuals as well as those with early signs of new onset cognitive impairment, AD, and other forms of dementia (e.g. FTD). Avid proposes that this combined data set of 600-700 subjects across all trials is an appropriate database to demonstrate the safety and effectiveness of ¹⁸F-AV-45 PET for the initial indication of imaging amyloid plaque pathology.

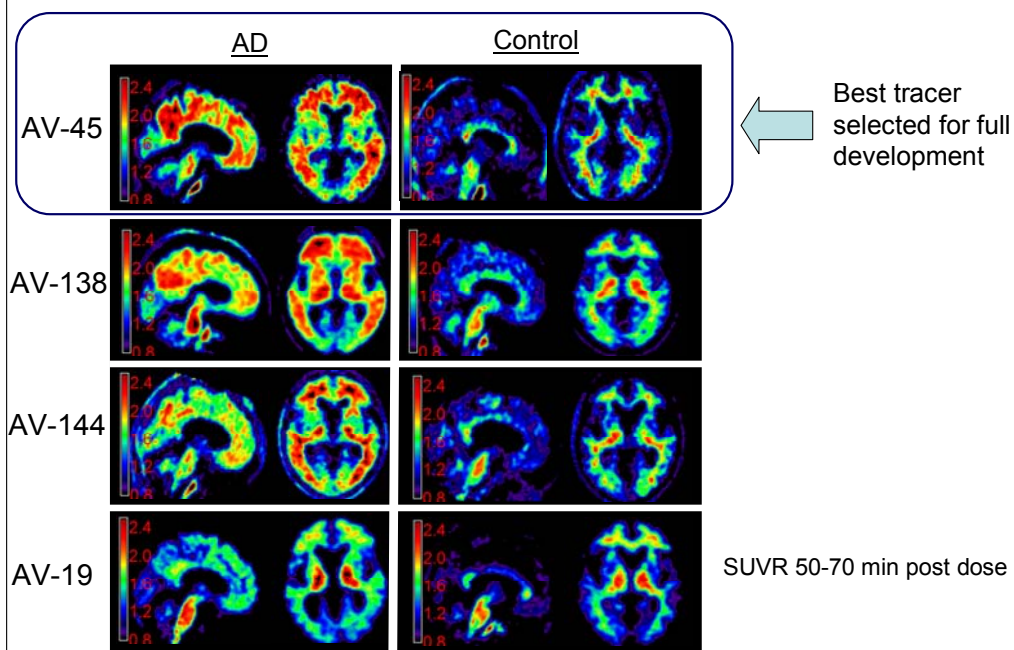
Beyond the initial NDA submission, Avid proposes to do additional well-controlled studies as Phase IIIb / IV trials to examine the utility of ¹⁸F-AV-45 PET for risk stratification and prognosis of populations at risk for progressing to AD, such as mild cognitive impairment (MCI) patients, as well as examine the use of ¹⁸F-AV-45 PET for identification of amyloid positive patients who would be most responsive to amyloid targeted therapies. Following initial NDA approval Avid will work with the FDA Office of Surveillance & Epidemiology, and professional societies and patient advocacy organizations to establish a registry of patient data containing ¹⁸F-AV-45 PET images. It is only through this mechanism that long term (5-10 year) studies and follow-up data can be generated. This, in turn, is expected to lead to further insight into the role of early amyloid plaque deposition in the brain in the epidemiology and risk factors associated with Alzheimer's disease.

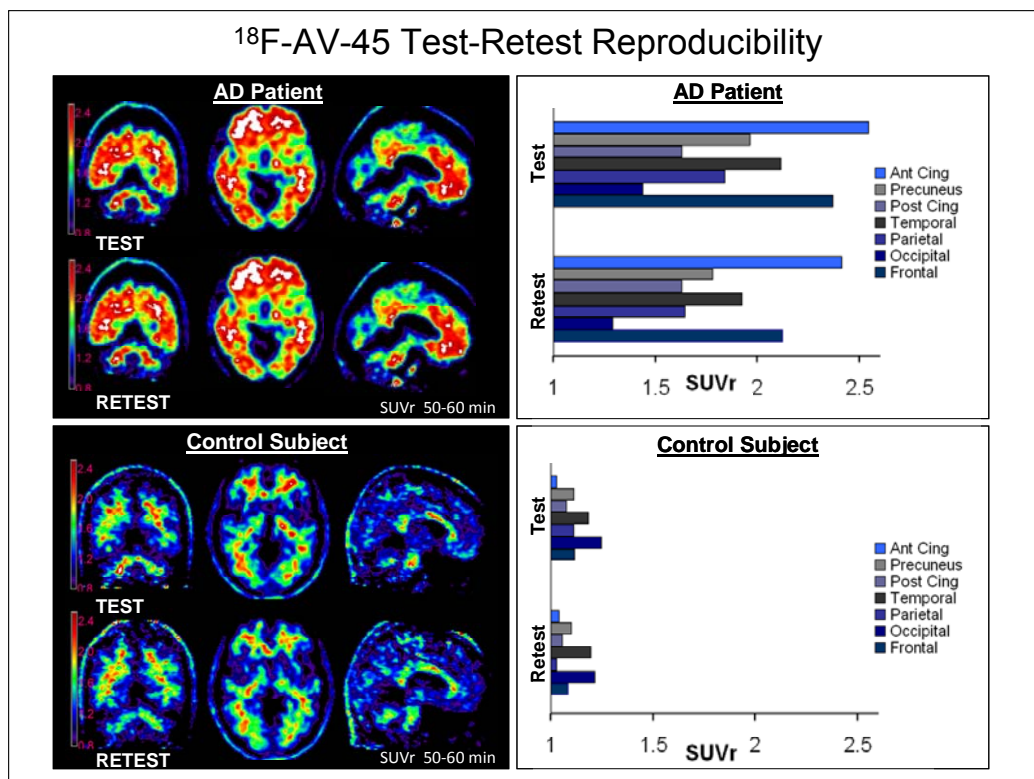
The Avid development proposal is summarized in the following slides. The subsequent sections of text provide details regarding Avid's development to date and future / proposed plans for ¹⁸F-AV-45 development.

¹⁸F-AV-45 Data Summary

- ¹⁸F-AV-45 selected as compound with best properties for amyloid imaging in comparative clinical trials under exploratory INDs
- >200 Subjects imaged with ¹⁸F-AV-45 so far
 - All subjects treated under IND
 - All subjects treated with standardized IND drug
 - World-wide production network being established
- Standardized methods established
 - Imaging procedure
 - Image analysis
 - IND-regulated drug production
- Clear separation of AD subjects from controls

¹⁸F-AV-45 Data: Selection under Exploratory INDs





Possible Reference Standards for Amyloid Pathology

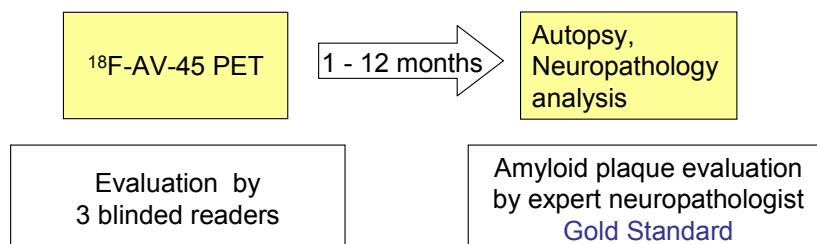
Method	Strengths	Weaknesses
Clinical assessment	Widely available and utilized	Low specificity No spatial information
CSF or blood biomarkers	Good research data available CSF markers track amyloid and tau peptides	Still in research stage Overlap between groups; high variability No spatial information
MRI volumetric measurements	Good research data available High anatomic resolution Spatial information on atrophy	Still in research stage Small differences Not AD specific
¹⁸ F-FDG PET	Good research data available Spatial information on hypometabolism	Does not measure primary pathology Not AD specific
¹¹ C-PiB PET	Good research data available Establishes potential of amyloid PET imaging	Still in research stage Non-IND studies & drug not approved Very short half-life of ¹¹ C limits use to expert centers
Histopathology	Defining pathology Widely accepted & endorsed Spatial correlation possible High precision measure	Technical challenges require novel trial designs to ensure feasibility

Proposed Phase III Autopsy Study

END-OF-LIFE STUDY

75 Terminally ill patients scanned with ¹⁸F-AV-45

30-50 expected autopsies and neuropathology



Part 1: 5 - 10 subjects
Imaging evaluation at time of autopsy
Define sample size and image analysis method.

Part 2: 25 - 40 subjects
Image evaluation at end of study
Pre-specified end-points

Proposed Phase III Autopsy Study

Image Evaluation

Qualitative read:

- Aβ+, Aβ-
- Blinded readers

Quantitative evaluation:

- SUV ratio to cerebellum (SUVr)
- Pre-established thresholds for + / -

Neuropathology

Qualitative read:

- CERAD rating (none/sparse/mod/freq)
- Blinded reader

Quantitative evaluation:

- Plaque count per high power field

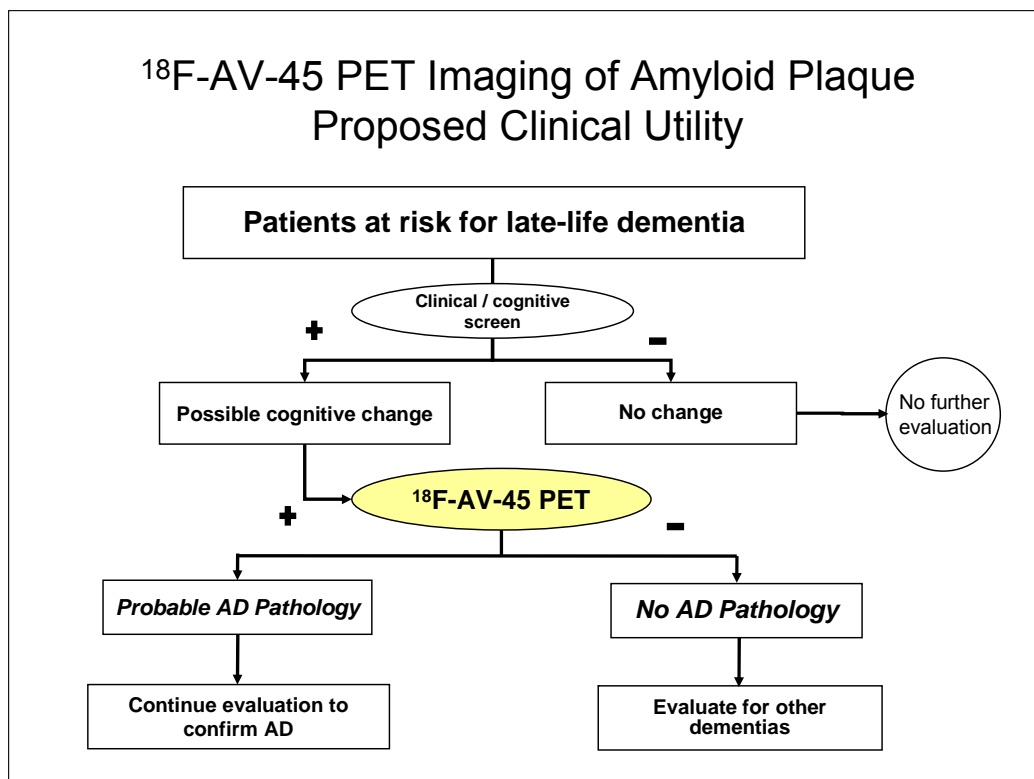


Key Outcome Variables

Negative Predictive Value (primary)

- Percentage of Aβ- PET scans that are none/sparse for amyloid pathology at autopsy

Correlation of SUVr to plaque counts (secondary)



Avid Proposal: Summary

- Use pathology as the primary reference standard
 - 1-2 year imaging to histopathology correlation study with 30-50 autopsies
- Seek initial approval based on
 - Imaging – histopathology correlation study
 - Supportive clinical and non-clinical data
 - Established negative predictive utility
- Follow with Phase IIIB / IV and registry studies
 - Long term clinical outcome and management changes
 - Establish positive predictive utility
 - Establish prognostic utility

2. QUESTIONS TO THE ADVISORY COMMITTEE

Avid would like the Advisory Committee (AC) to comment on the following general questions regarding development of an amyloid imaging agent:

1. Does the AC agree that correlation of PET scan results with histopathology at autopsy is an appropriate trial paradigm to demonstrate the effectiveness of a new imaging agent for visualizing amyloid pathology?
2. Does the AC agree with the proposed clinical utility of amyloid PET scanning: that is that a negative amyloid PET scan would be useful to rule out AD as a current diagnosis for the elderly subject presenting for evaluation of clinically identified progressive cognitive impairment?
3. Does the AC agree that large longitudinal Phase IV and post-approval registry trials are needed for determining the broader prognostic utility and clinical management outcomes from application of amyloid PET scanning?

3. BACKGROUND INFORMATION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, affecting approximately 5 million people in the US alone. However, diagnosis and treatment of the disease have been hampered by the absence of reliable non-invasive markers for the underlying pathology. Diagnosis based on consensus criteria (e.g. McKhann et al. 1984; American Psychiatric Association, DSM, 4th Edition, 1994) is approximately 81% sensitive and 70% specific by comparison to the gold standard of pathology at autopsy (Knopman et al. 2001). In addition to errors of misdiagnosis in patients with AD, there is significant under diagnosis, and approximately 10% of community dwelling elderly still have undiagnosed dementia (Solomon et al. 2000). Indeed, community physicians may fail to diagnose up to 33% of mild dementia cases (Lopponen et al. 2003). Thus, there is a need for a biomarker that can be applied in the community setting and can help physicians separate those patients who do not have AD from those who have pathological signs and should be evaluated further. Additionally, there are a large number of patients who, upon comprehensive diagnostic testing, are found to have cognitive impairment but are not demented and thus, do not meet diagnostic criteria for AD (e.g., patients with mild cognitive impairment, MCI). Some, but not all of these patients will go on to develop AD within 3-5 years (Petersen et al. 2001). A reliable biomarker might aid prognostic evaluation by documenting the presence or absence of AD related pathology.

Based on the definitions of AD endorsed by the American Academy of Neurology, American Psychiatric Association (DSM-IV) and others, patients without abnormal amyloid plaque levels do not meet currently accepted neuropathological criteria for AD (see Table 1). This definition of AD, which includes amyloid plaques as a required feature, is supported by more than 100 years of autopsy data (recent reviews listed in Table 1 below).

Therefore, based on this widely-endorsed definition of AD, the use of a test for ruling-out the presence of amyloid plaque pathology in subjects with clinical signs and symptoms of cognitive impairment will, effectively, rule-out the diagnosis of AD, and lead to more careful evaluation and appropriate treatment for alternative causes of cognitive deficits (e.g. Vascular dementia, dementia with Lewy bodies, Parkinson's dementia). Moreover, the use of a test for ruling-in the presence of abnormal levels of amyloid pathology in subjects with signs and symptoms of cognitive impairment will lead to the selection of patients who warrant more detailed work-up for the possible diagnosis of AD or MCI.

A variety of biomarkers for amyloid plaque accumulation have been proposed (Thal et al. 2006). In contrast to techniques designed to indirectly estimate levels of brain amyloid plaques from A β levels in plasma or cerebral spinal fluid, imaging techniques utilizing radiolabeled PET tracers that bind to the aggregated A β peptides in amyloid plaques have the potential to directly assess brain amyloid pathology. One approach has utilized the ¹¹C-labeled PET tracer 6-OH-BTA ([*N*-methyl-]²-(4'-methylaminophenyl)-6-hydroxybenzothiazole) also known as Pittsburgh compound B or PIB (Klunk et al. 2001, 2004, 2005). ¹¹C-PIB studies have shown that higher levels of radioactivity can be detected by PET in the cortex of patients with AD than in the cortex of healthy controls, presumably reflecting the elevated accumulation of A β pathology and consequent binding of ¹¹C-PIB in the cortex of patients with AD (Lopresti et al. 2005). However, ¹¹C-PIB has not been validated in a prospective study comparing imaging results to histopathological measurements of amyloid plaque in the brain.

Despite the encouraging results in multiple academic studies of ¹¹C-PIB, the short half-life (20 minutes) of the ¹¹C isotope limits its utility as a tool for community based diagnostic testing and therapeutic evaluation or as a tool for large scale clinical trials. In contrast, the amyloid binding agent ¹⁸F-AV-45 (Zhang et al. 2007) is labeled with ¹⁸F. Since ¹⁸F has a radioactive half-life of 110 minutes, regional preparation and shipping of doses is possible, thereby increasing the availability to a larger number of potential imaging centers that could perform such a test. Indeed ¹⁸F-AV-45 is already being produced under Avid's IND at regional manufacturing hubs that can supply the tracer to imaging sites in proximity to a significant proportion of the U.S. population. Avid plans to validate ¹⁸F-AV-45 as a measure for amyloid pathology by conducting a prospectively-designed Phase III trial of ¹⁸F-AV-45 PET versus autopsy-based histopathological measurements of amyloid plaque in a standardized fashion and in accordance with accepted pathological criteria.

Preclinical and clinical studies conducted to date suggest that ¹⁸F-AV-45 has the potential to serve as an agent for in-vivo imaging of Aβ pathology in humans with signs of late-life progressive cognitive impairment. FDA guidance documents for the development of medical imaging drugs suggest that indications for use may be based on a demonstrated ability to image disease pathology (*Guidance for Industry: Developing Medical Imaging Drug and Biological Products, Part 2. Clinical Indications*, June 2004).

Table 1. Definitive diagnosis of AD

Organization	Reference	Guideline
American Psychiatric Association	APA Practice Guideline for the Treatment of Patients with AD and Other Dementias, 2 nd Ed., Rabins et al., 2007.	Definitive diagnosis requires clinical and pathological findings: “A definitive diagnosis of AD requires both the clinical syndrome and microscopic examination of the brain at autopsy, at which time the characteristic plaques and neurofibrillary tangles widely distributed in the cerebral cortex will be seen.”
American Psychiatric Association	DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4 th Ed., 2000.	Definitive diagnosis requires pathological confirmation: “Because of the difficulty of obtaining direct pathological evidence of the presence of AD, the diagnosis can be made only when other etiologies of dementia have been ruled out.”
United States Department of Health and Human Services	Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on AD, McKhann et al., 1984	Definitive diagnosis requires clinical and pathological findings: “Criteria for diagnosis of DEFINITE Alzheimer’s disease are: the clinical criteria for probable Alzheimer’s disease and histopathologic evidence obtained from a biopsy or autopsy.” “A diagnosis of definite AD requires hisopathologic confirmation.”
American Academy of Neurology	Practice Parameter: Diagnosis of dementia (an evidence-based review): Report of the Quality Standards Subcommittee, Knopman et al., 2001.	Neuropathology is the gold standard for diagnosis: “There are 13 studies, 3 Class I and 10 Class II, that have addressed the diagnostic accuracy of the clinical diagnosis of AD using neuropathologic confirmation as the ‘gold standard’.”
American Geriatrics Society	Clinical Practice Guidelines: Early Detection of Dementia, 2002.	Definitive diagnosis requires clinical and pathological findings: Guidelines are abstracted from the American Academy of Neurology’s dementia guidelines, described above. “The NINCDS-ADRDA criteria ... should be routinely used”
College of American Pathologists (under auspices of AMA)	Practice Guidelines for Autopsy Pathology, James Powers, Arch Pathol Lab Med, 1995.	Definitive diagnosis requires presence of amyloid plaques: “This grade [of plaques] is then correlated with the patient’s age to arrive at an age-related plaque score, which is combined with the clinical history (presence or absence of dementia) to determine the diagnosis.”
CERAD (Consortium to Establish a Registry for AD)	The Consortium to Establish a Registry for AD. Part II. Standardization of the neuropathologic assessment of AD, Mirra et al., Neurology, 1991.	Definitive diagnosis requires high (age-adjusted) abundance of amyloid plaques: “The age-related plaque score is integrated with the presence or absence of a clinical history of dementia to arrive at a diagnostic level of certainty with regard to AD.”
National Institute on Aging & Reagan Institute Working Group	Consensus Recommendations for the Postmortem Diagnosis of Alzheimer’s Disease, Neurobiology of Aging, 1997.	Definitive diagnosis requires high (age-adjusted) abundance of amyloid plaques and neurofibrillary tangles: “There is a high likelihood that dementia is due to AD lesions when the postmortem brain shows the presence of both neuritic plaques and neurofibrillary tangles in neocortex.” There is a low probability of AD in subjects with low levels of amyloid plaques: “There is a low likelihood that dementia is due to Alzheimer’s disease lesions when the postmortem brain shows neuritic plaques and neurofibrillary tangles in a more limited distribution and/or severity (i.e. CERAD infrequent, and Braak and Braak Stage I/II).”

5. SUMMARY OF PRECLINICAL DATA

Summary of Selected Pharmacology Experiments

Amyloid Binding Assays (Human)

Method: Competitive binding assay on AD post-mortem brain homogenates using cold AV-45 as the test substance and ¹²⁵I-IMPY (a compound previously shown to be specific for A β amyloid) as the hot ligand.

Results:

$$K_i = 5.5 \pm 0.7 \text{ nM}$$

Method: Direct binding assay on AD post-mortem brain homogenates using hot ¹⁸F-AV-45 as the test substance. K_d and B_{max} were calculated by Scatchard plot and Rosenthal analysis.

Results:

$$K_d = 3.1 \pm 0.7 \text{ nM}$$

$$B_{max} = 2.3 \text{ pmol/mg}$$

Conclusions: ¹⁸F-AV-45 shows high affinity specific binding to amyloid pathology.

Amyloid Plaque Section Labeling (Human)

Method: Frozen sections of AD and control post-mortem brain tissue were incubated with hot ¹⁸F-AV-45 in PBS, washed and exposed to film. Adjacent sections are stained with antibodies specific for A β .

Results:



AD Section



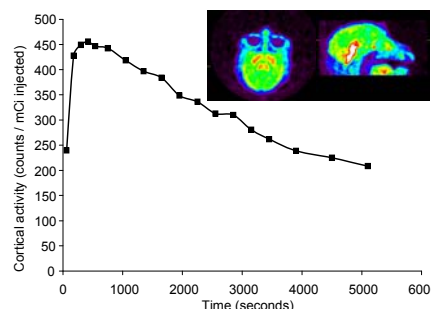
Control Section

Conclusions: ¹⁸F-AV-45 shows specific labeling to amyloid pathology. No labeling of tau pathology or other neurodegenerative lesions is detected.

Brain Uptake and Clearance (Rhesus Monkey)

Method: An anesthetized rhesus monkey was injected with a 5 mCi bolus of ¹⁸F-AV-45; the brain was continuously imaged by microPET and tissue time-radioactivity curves were generated for cortical brain regions.

Results:



Conclusions: ¹⁸F-AV-45 shows excellent brain uptake with rapid wash-out.

Summary of Selected Safety Pharmacology and Toxicology

CNS and Cardiovascular Receptor Binding	
Method: Off-target AV-45 binding was assessed by competitive binding assays against a panel of 46 CNS and cardiovascular receptor binding sites.	Results: No high affinity ($K_i < 1 \text{ uM}$) interaction at any binding site
Cardiovascular and Respiratory Safety Pharmacology	
Method: Cardiovascular safety and respiratory functions were tested in beagle dogs implanted with subcutaneous telemetry units to monitor cardiac and respiratory functions, and given doses of AV-45 up to 100x MHD.	Results: No adverse effects observed at any dose level.
Method: Cardiovascular safety pharmacology was studied using cloned hERG potassium channels expressed in human embryonic kidney cells as per FDA guidelines.	Results: No significant inhibition of hERG/ I_{Kr} current at any dose level.
Central Nervous System Safety Pharmacology	
Method: CNS safety pharmacology was tested in rats at single acute doses of up to 100x the intended maximal intended human dose (MHD, scaled allometrically) and at prolonged exposure of 28-day daily dosing at up to 25x MHD. A standard functional observational battery (FOB) was employed to assess any CNS effects.	Results: No observed effects at any dose level.
Acute and Repeat Dose Toxicity in Rats and Dogs	
Method: The potential toxicity of AV-45 was tested in rats with single acute and repeated doses at multiples (up to 100x) of MHD. In addition, a repeat-dose intravenous toxicity study in beagle dogs was performed.	Results: No clinically relevant adverse effects at any dose level.
In-Vivo Genotoxicity	
Method: In-vivo micronucleus assay was performed at doses up to 83X MHD exposure in up to 3 repeated administrations.	Results: No evidence of genotoxicity.

6. ¹⁸F-AV-45 CLINICAL PROGRAM

a. Safety

Clinical studies of ¹⁸F-AV-45 Injection have included baseline and post-dose assessments of adverse events, vital signs, ECG, and blood and urine clinical chemistries. In clinical studies performed in more than 200 subjects to date there have been only a few scattered adverse events, the majority of which are likely procedural related (e.g. claustrophobia and backache have been among the most common adverse events). All of these adverse events have been mild and resolved spontaneously, with the exception of a single serious AE, which was considered not drug-related; a patient tripped and fell 4 days post-drug administration and suffered moderate trauma.

b. Completed and ongoing clinical studies

¹⁸F-AV-45-A01: Proof-of-concept brain imaging trial

The first, proof-of-concept, clinical study of ¹⁸F-AV-PET imaging was conducted in a total of 32 subjects. Study ¹⁸F-AV-45-A01 evaluated brain uptake, biodistribution, pharmacokinetics, metabolism, and safety of ¹⁸F-AV-45 in healthy elderly volunteers and patients with AD.

Figure 2 shows a typical image from a patient with AD and a cognitively normal control. These images were obtained in a 10 minute acquisition beginning 50 minutes following administration of ¹⁸F-AV-45. As expected, the patient with AD showed selective retention of tracer in cortical areas expected to be high in amyloid plaque, whereas healthy elderly controls showed rapid wash out from these areas, with only minimal cortical tracer retention. Both AD and healthy controls showed similarly rapid wash out in cerebellum (a region typically devoid of amyloid plaques) and relatively low levels of non-specific tracer retention in white matter areas.

For quantitative analysis the images were co-registered with the individual's magnetic resonance imaging (MRI), then spatially normalized to a stereotaxic atlas. Volumes of interest for the cortex and cerebellum were overlaid on the respective images and counts extracted.

Standard uptake values (SUVs) were calculated for multiple regions including the frontal cortex, precuneus and cerebellum and SUV ratios (SUVRs) were calculated as frontal cortex/cerebellum, and precuneus/cerebellum. Figure 3 shows the time activity curves for the frontal cortex, precuneus and cerebellum for the two subjects shown in Figure 2. Consistent with the interpretation of the images, the time activity curves show a clear separation between cortical and cerebellar activity for the patient with AD, but not for the cognitively normal control. The kinetics of brain uptake and washout are favorable for ¹⁸F-AV-45 PET imaging of amyloid plaque in less than 1 hour after injection.

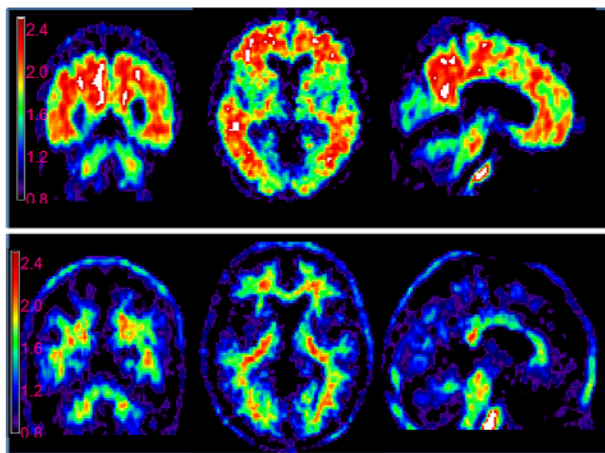


Figure 2: Average of two consecutive 5 minute PET brain images (obtained 50 – 60 minutes post injection) from an AD patient (top) and healthy control (bottom), following injection with 10 mCi ^{18}F -AV-45. Experimental conditions were identical for the two subjects. Images are scaled as count ratios (SUVRs) for each voxel relative to the average of the cerebellum grey matter.

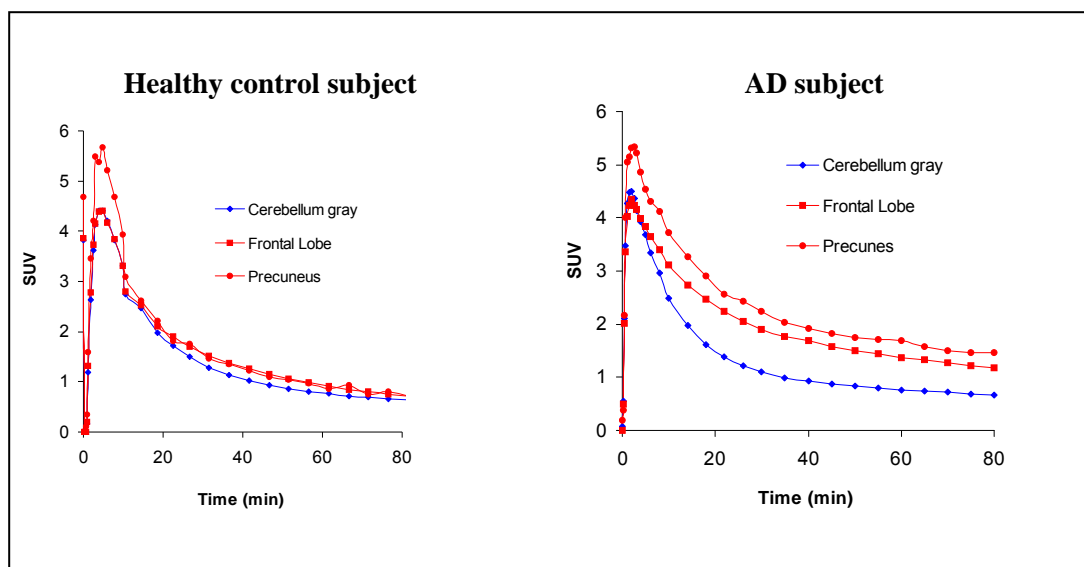


Figure 3: Standard uptake values (SUV) for frontal cortex, precuneus and cerebellum, for a representative healthy control and patient with AD. The time activity curves show a clear separation between cortical and cerebellar activity for the patient with AD in less than 30 minutes after injection, but not for the cognitively normal control.

¹⁸F-AV-45-A02: Human PK and radiation dosimetry

Study ¹⁸F-AV-45-A02 evaluated whole body biodistribution and radiation dosimetry of a 370 MBq (10mCi) dose of ¹⁸F-AV-45 in 9 healthy volunteers over a period of up to 6 hours following injection. Based on these data, the organs with highest exposure were the liver and gallbladder wall. The human effective dose was approximately 0.036 mSv/MBq or 13.3 mSv (1.3 rem) for a 370 MBq (10 mCi) dose, which is in the range of the values observed with other ¹⁸F-labeled compounds such as ¹⁸F-Fluorodeoxyglucose (FDG).

¹⁸F-AV-45-A03: Dose ranging trial

The ¹⁸F-AV-45-A03 study examined the safety and PET image quality for a low-level (110 MBq / 3mCi) and moderate-level (370 MBq / 10 mCi) dose of ¹⁸F-AV-45 Injection in healthy control subjects and AD patients (20 subjects total). Preliminary analysis has shown that high quality PET images can be acquired with 5 - 10 minutes image acquisition time with 110 - 370MBq of ¹⁸F-AV-45. This short imaging period is helpful to minimize the confounding effects of patient motion which can occur over longer imaging periods.

¹⁸F-AV-45-A04: PET imaging reproducibility study

The ¹⁸F-AV-45-A04 study examined the safety and reproducibility of ¹⁸F-AV-45 PET images acquired on different days in the same subjects. This study was conducted in healthy volunteers as well as subjects with Alzheimer's disease (20 subjects total, each imaged twice). SUV ratios to cerebellum were measured in target cortical regions for 5 minute images from each of the test and the retest sessions. Test/retest variability (calculated as absolute difference of test minus retest, divided by test) was 5% ($\pm .03$) for AD subjects and 3% ($\pm .02$) for healthy controls. The correlation coefficient between test and retest was 0.99 ($\pm .01$) for AD subjects and 0.98 ($\pm .02$) for healthy controls. These data confirm that ¹⁸F-AV-45 is a highly reliable measure with excellent consistency from day-to-day.

¹⁸F-AV-45-A05: PET imaging of AD, MCI and Control subjects

The ¹⁸F-AV-45-A05 study is examining the safety and preliminary efficacy of ¹⁸F-AV-45 PET imaging for the differentiation of healthy control subjects from those subjects with mild cognitive impairment or Alzheimer's disease. This study is still ongoing and is expected to complete enrollment by the end of the year (180 subjects total).

¹⁸F-AV-45-A08: PET imaging of AD and FTD subjects

Additional studies of ¹⁸F-AV-45 are to be conducted to examine safety and preliminary efficacy for detecting amyloid plaque pathology in a mixed population of Alzheimer's and Frontal-temporal dementias. These studies are being conducted to examine the ability of ¹⁸F-AV-45 PET to distinguish dementia subjects with and without A β plaque pathology.

c. Proposed pivotal clinical study

¹⁸F-AV-45-A07: PET imaging correlation with autopsy histopathology

This study is designed to test the relationship between the absence or presence of neuritic amyloid plaques levels, as assessed by ¹⁸F-AV-45 PET imaging, and neuritic amyloid plaque burden, as assessed by histopathology at autopsy. Approximately 50-75 subjects with terminal medical conditions (anticipated life expectancy ≤ 6 months as determined by the principal investigator) will be enrolled in this trial. It is intended that approximately one-third (33%) of the subjects enrolled should have a diagnosis of AD. Subjects will receive a single i.v. bolus of 370 MBq (10 mCi) of ¹⁸F-AV-45 followed by brain PET imaging for 10 minutes duration, beginning approximately 50 minutes post-injection. Images will be evaluated qualitatively and quantitatively. Images will be visually examined by three independent nuclear medicine specialists blinded to the clinical data and will be classified as A β + (amyloid positive, AD-like) or A β - (amyloid negative, not AD). Regional assessments will also be made. For quantitative evaluation, standard uptake values (SUVs) will be calculated for target areas drawn to correspond closely with the regions of interest for autopsy sampling. SUVR will be calculated for cortical target areas relative to the cerebellum.

Subjects or caregivers will be asked to provide consent for participation in a local brain donation program. Neuropathological assessment will minimally follow the CERAD guidelines. Frequency of amyloid plaques in sections from CERAD specified neocortical regions of brain (superior-middle temporal gyrus, middle frontal gyrus, inferior parietal lobule, and anterior cingulate gyrus) will be evaluated semi-quantitatively (none, sparse, moderate or frequent) and quantitatively, as number of neuritic amyloid plaques per high powered field.

The primary analysis will determine the correspondence between the classification of over-all low cortical amyloid burden by ¹⁸F-AV-45 PET imaging (A β -) and autopsy evaluation of over-all plaque burden (none/sparse). The primary analysis will focus on patients who come to autopsy within 12 months of PET imaging, because the link between the imaging data and the autopsy result may be less certain as neurodegeneration continues over time. Secondary analyses will determine the degree of correlation between regional plaque burden as measured by imaging (both qualitative image interpretation and quantitative image analysis using cortical to cerebellar SUVR [Standard Uptake Value Ratio]) and by pathology (semi-quantitative and quantitative amyloid plaque assessments).

Proposed supportive clinical study

¹⁸F-AV-45-A06: PET imaging in subjects presenting for evaluation of cognitive impairment

All patients presenting for first diagnostic evaluation of cognitive impairment, who do not have obvious causes for their cognitive impairment (e.g. onset coincides with recent head trauma or stroke), will be eligible to participate. ¹⁸F-AV-45 PET images will be evaluated qualitatively and quantitatively by qualified blinded readers. The enrolling physician will provide all clinical data, including a diagnosis recommendation, to an expert consensus panel. The consensus panel will then make a consensus diagnosis: AD (probable or possible), MCI or not AD (no impairment or other dementia). The agreement between the blinded reader assessment of amyloid-burden on the PET scan versus the expert consensus panel A β (+) and A β (-) will be determined.

7. ¹⁸F-AV-45 PROPOSED CLINICAL INDICATION AND DEVELOPMENT: OVERVIEW AND RATIONALE

a. Overview of Development Plan

Reflecting the FDA guidance and the consensus view from the expert scientific community (e.g. McEwan et al., 2007; Dubois et al., 2007; McKhann et al., 1984), Avid proposes that the development plan for ¹⁸F-AV-45 focus on demonstrating the ability to image amyloid pathology. Phase II and III studies are proposed to establish that ¹⁸F-AV-45 effectively detects (or rules out) amyloid plaque pathology in the human brain. The proposed development pathway will provide support to an indication such as the following: ***“¹⁸F-AV-45 is indicated for PET imaging of amyloid plaque pathology in the brain to aid in the evaluation of patients with signs or symptoms of cognitive impairment.”*** Avid proposes a single well-controlled Phase III trial to support the above target indication (trial ¹⁸F-AV-45-A07). This trial is based on the comparison of ¹⁸F-AV-45 PET imaging to post-mortem histopathology as the reference standard (“standard of truth”) for the presence/absence of amyloid plaque pathology. Histopathology has been well documented as a standard assessment for the presence or absence of amyloid plaque pathology (see Table 1). In fact, the definition of Alzheimer’s disease is established based on histopathological findings of amyloid plaque in the brains of subjects with dementia (Mirra et al., 1991).

Supportive clinical trials to the above histopathology correlation study, include trials A05, A06 and A08. Trials A05 and A08 are conducted in well characterized populations of AD, MCI healthy controls and frontal temporal dementia (FTD) subjects. The aim of these trials is to show that the expected ¹⁸F-AV-45 PET scan positivity rate and negativity rates are observed for the respective populations of subjects which are high probability Aβ(+) (e.g. AD), intermediate probability Aβ(+) (e.g. MCI), and high probability Aβ(-) (healthy controls or FTD).

Based on the proposed indication ¹⁸F-AV-45 will be used in ruling-in or ruling-out the presence of amyloid plaque pathology in the brains of living subjects with cognitive impairment. The primary clinical utility proposed for ¹⁸F-AV-45 would be in the case of a negative PET scan, where the presence of amyloid plaque pathology can be excluded at the level of what is considered histopathologically abnormal (as defined by CERAD and NIA-Reagan Institute criteria). A positive scan (for the presence of amyloid plaque) would also be useful as support to the further clinical and imaging evaluation of a patient suspected of having AD (i.e. additional diagnostic work-up is warranted).

Avid proposes to file its initial NDA based on the Phase III autopsy-based histopathology correlation trial together with the supportive trial data in highly selected populations of AD, MCI, FTD and normal subjects.

Beyond the initial utility described here (mainly based on the value of a negative scan), large longitudinal studies are critically needed to fully establish the clinical utility of amyloid imaging. These studies can only practically be accomplished post-approval. Avid will continue to conduct long-term Phase IIIb, Phase IV and registry studies to establish positive predictive utility and prognostic utility over a five to ten year period subsequent to initial NDA approval.

b. Clinical Utility for Assessing Amyloid Plaque Status

A number of studies have addressed the prevalence of various causes of dementia (as confirmed by histopathology). AD is the most common cause of dementia, but accounts for only approximately 64% to 77% of all cases of dementia (Table 3).

Table 3. Frequency of AD in unselected dementia series, confirmed by histopathology.

Reference	<i>n</i>	AD or AD + other diagnosis ¹	Non-AD diagnoses (pooled) (%)
Jellinger et al., 1990	675	77%	23%
Brunnstrom et al., 2008	524	64%	36%
Victoroff et al., 1995	196	76%	24%

¹ This includes patients with a diagnosis of mixed dementia, e.g. AD + Vascular dementia or AD + DLB.

Patients with non-AD causes of dementia are frequently misdiagnosed with AD and the specificity of a diagnosis of probable AD is approximately 70% (Knoppman et al., 2001). Peer reviewed literature confirms that approximately 10 – 23% of all patients that receive a diagnosis of AD do not have AD pathology at autopsy (Table 4, below).

In each of these studies, no patients received a diagnosis of neuropathologically confirmed AD unless they had amyloid plaque. Thus, in these studies the NPV of amyloid assessment was 100%. In only rare cases did any of the non-AD dementia subjects have any more than sparse neuritic plaques (2 subjects in Gearing et al., and 3 in Wade et al., Table 4), suggesting that amyloid plaque burden also has nearly 100% specificity for AD in a dementia population.

By assessing amyloid burden with an imaging test, such as ¹⁸F-AV-45 PET, in patients who are being worked up for possible AD, it may be possible to eliminate AD as a potential diagnosis for patients who are truly amyloid negative. A proposed diagnostic algorithm to incorporate an amyloid plaque assessment is shown in Figure 4 below.

Table 4. Frequency of false positive clinical diagnosis of AD, confirmed by autopsy

Study	Summary	False Positive Rate of Clinical Dx
Lim et al., <i>J Am Geriatr Soc.</i> 1999; 47:564-569.	Of 100 patients with clinical diagnosis of possible or probable AD followed to autopsy, 20 had a final diagnosis that did not include AD – none of these had NPs.	20% of patients with “possible or probable AD” did not have AD at autopsy.
Victoroff et al., <i>Am J Psychiatry</i> 1995; 152:1476-1484.	Of 163 patients with clinical diagnosis of possible or probable AD followed to autopsy, 29 had a final diagnosis that did not include AD – none of these had NPs.	18% of patients with “possible or probable AD” did not have AD at autopsy.
Klatka et al., <i>Arch Neurol.</i> 1996; 53:35-42.	Of 170 patients with clinical diagnosis of possible or probable AD followed to autopsy, 21 had a final diagnosis that did not include AD – none of these had NPs.	12% of patients with “possible or probable AD” did not have AD at autopsy.
Wade et al., <i>Arch Neurol.</i> 1987; 44:24-29.	Of 55 patients with clinical diagnosis of DAT or DAT + MID followed to autopsy, 10 had a final diagnosis that did not include AD (3 of these 10 had some senile plaques).	18% of patients with “DAT or DAT + MID” did not have AD At autopsy.
Pearl el a., <i>S Med J</i> , 1997; 90: 720-722.	Of 234 patients with clinical diagnosis of AD or mixed AD followed to autopsy, 53 patients had a final diagnosis that did not include AD – none of these had NPs.	23% of patients with AD or AD + vascular dementia did not have AD at autopsy.
Mayeux et al., <i>NEJM</i> 1997; 338:506-511	Of 1833 patients with clinical diagnosis of probable AD followed to autopsy, 190 did not have AD at autopsy.	10% of patients with clinical AD did not have AD at autopsy.
Jobst et al., <i>Int. Psy Ger</i> 199; 10:271-302	Of 92 patients with clinical diagnosis of probable or possible AD followed to autopsy, 15 did not have AD at autopsy	16% of patients with clinical AD did not have AD at autopsy.
Massoud et al., <i>Arch Neurol</i> 1999; 56: 1368-1373.	Of 60 patients with clinical diagnosis of probable or possible AD followed to autopsy, 6 did not have AD as a neuropathologic diagnosis. None of these had NPs	10% of patients with possible or probable AD did not have AD at autopsy.
Raginwala et al., <i>Am J Geriatr Psych</i> 2008; 16: 384-388.	Of 225 subjects with a clinical diagnosis that included AD followed to autopsy, 31 did not have AD as a neuropathologic finding. All were plaque negative.	14% of patients with AD as a clinical diagnosis to do not have AD at autopsy.
Gearing et al., <i>Neurology</i> 1995; 45: 461-466.	Of 106 patients with clinical diagnosis of probable or possible AD followed to autopsy, 14, did not have AD as the neuropathologic diagnosis (2 of the 14 had moderate senile plaques)	13% of patients with possible or probable AD did not have AD at autopsy.

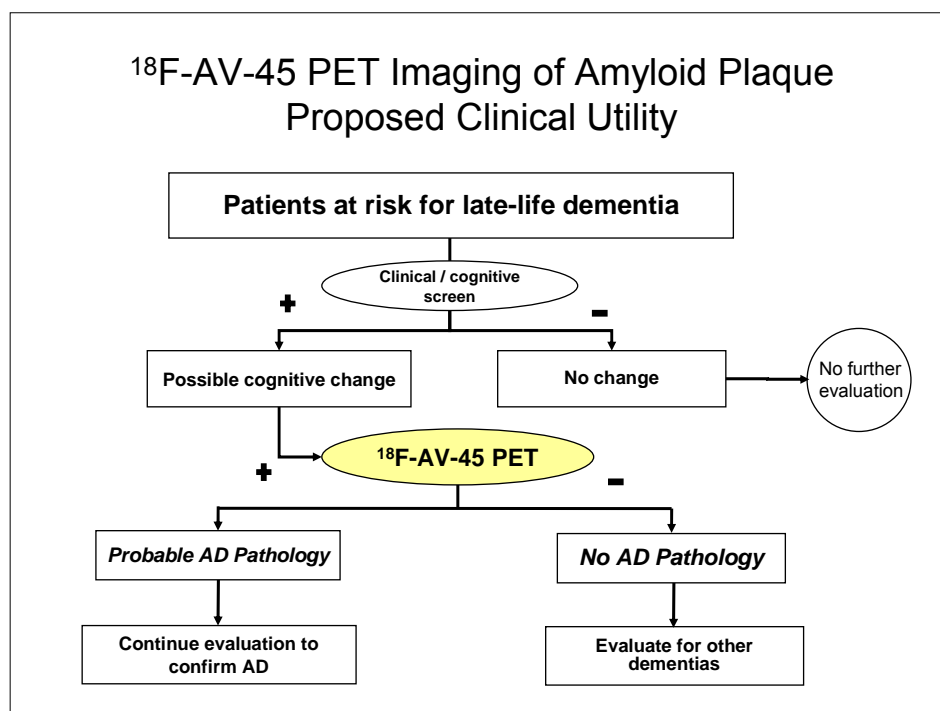


Figure 4: Clinical utility of ¹⁸F-AV-45 imaging.

A hypothetical example showing how this algorithm could be utilized (where an accurate assessment of amyloid status (+/-) is available from an amyloid plaque PET scan) is shown using data from Lim et al, in Figure 5 below. In the top 2 x 2 table (below) are the actual diagnostic results. In this study, of 100 patients with a clinical diagnosis of AD, 20 did not have any amyloid plaques at autopsy and received a final diagnosis other than AD. If it had been possible to assess amyloid plaques premortem, all of these 20 patients could have been reclassified as non-AD dementia (as shown in the lower table of Figure 5). This would have increased both specificity and NPV and overall accuracy of clinical diagnosis.

		Definite (neuropathological) AD (or AD + other dx)		
		+	-	
Probable or possible AD (or AD + other dx)	+	80	20	100
	-	14	20	34
		94	40	134

Sens = 0.85	PPV = 0.80
Spec = 0.50	NPV = 0.59
Acc = 0.75	

Lim et al., *J Am Geriatr Soc.* 1999; 47:564-569.

Use amyloid assessment to exclude NP negative subjects from AD group

Probable or possible AD (or AD + other dx)

	+	-	
+	80	20	80
-	14	40	54
	94	40	134

Definite (neuropathological) AD (or AD + other dx)

Sens = 0.85	PPV = 1.0
Spec = 1.0	NPV = 0.74
Acc = 0.90	

Figure 5: Consequences of ^{18}F -AV-45 imaging for diagnostic accuracy of AD.

Note that while the NPV for an accurate amyloid assessment is 100% (i.e. there can be no false negatives since subjects cannot lack amyloid plaques and still have AD) the NPV for clinical assessment including amyloid assessment according to the above algorithm does not reach 100% because patients who have amyloid plaques may still be classified as non-AD by the clinician. Specificity however can reach 100% because patients who do not have plaques are eliminated from the false negative group.

Correctly eliminating AD from the differential diagnosis for subjects in the population of those with uncertain etiology of dementia is clinically useful for patient management purposes. Specifically, patients who do not have A β pathology (not-AD): (1) should undergo further diagnostic testing to elucidate the real cause of dementia; (2) have a different prognosis than those with AD; and (3) should receive therapeutic management appropriate for their specific diagnosis.

c. Selection of Reference Standard

Histopathology as the Primary Reference Standard for Amyloid Plaque Detection

In the planned Phase III trial (the A07 trial) we propose to use autopsy confirmation of neuritic amyloid plaque pathology (according to CERAD criteria) as the primary reference standard for testing the efficacy of ¹⁸F-AV-45 as a marker for amyloid plaque pathology in the brain. We propose this reference standard for the following reasons:

1. Post-mortem histopathology is uniformly considered the gold standard for establishing presence or absence of amyloid plaque pathology.
2. Histopathological evidence of amyloid plaque pathology is a required component for the definitive diagnosis of AD (i.e. amyloid plaque pathology has a 100% NPV for ruling out AD).
3. A large number of peer-reviewed studies provide validated methods for histopathological determination of amyloid plaque pathology.

Because of practical considerations this pivotal study will have two significant limitations. First, the sample size for this study will be relatively small. It is not feasible to prospectively conduct autopsy studies in hundreds of patients who have been imaged with a new PET tracer. Second, the population studied (terminally ill patients) will be different than the population in whom ¹⁸F-AV-45 will be used (symptomatic patients being evaluated for AD). This is necessary because most patients presenting for evaluation of AD will not die within 1 year of their clinical assessment and during a prolonged follow-up period between imaging and autopsy there may be changes in a patient's amyloid status or burden that would cloud correlation between imaging and pathology. Nevertheless, the proposed study will include patients with a range of cognitive function, from cognitively normal, to MCI, to dementia, including AD and may include patients with cognitive impairment due to conditions other than AD pathology. Thus, the population in the autopsy study will approximate the target population with respect to their range of cognitive impairment, differing primarily in the presence of a concomitant terminal medical condition.

Both of the above limitations of the histopathology correlation study will be addressed by supplementing this study data with larger trials to be performed in well-defined Aβ(+) and Aβ(-) dementia populations (trials -A05, -A06, -A08, -A10).

Feasibility of Using Histopathology as a Primary Reference Standard

Several studies in the peer reviewed literature have used histopathology as a reference standard for validation of imaging tests for neurodegenerative disease. Particularly relevant to our proposal are studies done for validation of ¹⁸F-FDG for evaluation of dementia (e.g. Silverman et al., 2001; Jagust et al., 2007), for ¹²³I-FP-CIT for evaluation of dopaminergic degeneration in dementia with Lewy bodies (e.g. Walker et al., 2007) and for MRI for evaluation of neuropathological correlates of dementia (e.g. Jagust et al., 2008). These studies are summarized in Table 5 below.

Table 5. Literature studies using histopathology as a reference standard for imaging tests in dementia patients.

Reference	Design	Sample size	Timeline
Silverman et al., 2001	A cohort of patients had ¹⁸ F-FDG PET studies while undergoing evaluation for dementia as part of various research protocols. Those who later had histopathology follow-up were selected for analysis. Scans were centrally re-read by blinded reviewers.	n=138	Images were acquired over a 16 year period. Mean time to autopsy was 2.9 years.
Walker et al., 2007	A cohort of 61 subjects with a clinical diagnosis of DLB or other dementia underwent ¹²³ I-FP-CIT scan. Those who later had histopathology follow-up were selected for analysis.	n=20	Images were acquired over a 10 year period. Mean time to autopsy was 2.8 years.
Jagust et al., 2007	A cohort of with dementia, cognitive impairment or normal cognition underwent ¹⁸ F-FDG PET; 44 subjects were followed to autopsy and included for analysis.	n=44	Images were acquired over an 8 year period. Mean time to autopsy was 4.9 years.
Jagust et al., 2008	A cohort of 704 subjects drawn from various studies underwent MRI imaging; 127 were followed to autopsy and were included for analysis.	n=127	Images were acquired over a 12 year period Mean time to autopsy from last imaging session was 2.7 years (pts had repeat MRIs every 2 – 4 years).

These studies suggest that it is possible to conduct a trial that incorporates autopsy follow-up as a reference standard for validation of an imaging test. However there are two important caveats from these studies: first, all required 10 or more years to acquire sufficient numbers of imaging / autopsy correlations; and second, mean time from last imaging session to autopsy was approximately 3 years.

Practical considerations preclude decade-long trials in commercial development of novel imaging agents. For this reason we have proposed a relatively small sample size in the pivotal -A07 trial (30 – 50 subjects autopsied). The power of this study may be increased by analyzing various brain regions in individual patients as separate measures. However these are not independent outcomes and region by region statistical analysis must be undertaken with caution. Although one would anticipate achieving a very high association between ¹⁸F-AV-45 scans read as negative and neuritic plaque counts of none to sparse on autopsy (i.e. NPV \geq 90%), a sample size of ~ 30-50 subjects is projected to provide a confidence interval for NPV ranging from 70 – 100%.

A mean of 3 years time between image acquisition and obtaining the reference standard is not appropriate for a trial designed to test a pathological indication (i.e. imaging amyloid plaques), since pathological status may change over this time interval. For this reason Avid proposes to use an end-of-life design for the pivotal -A07 study. In this study the

time between image and autopsy will be limited to 1 year or less. Since this trial will enroll patients with limited life expectancy, it is expected that the time from autopsy to completion of study will be significantly shorter than the above-referenced studies. However, we are not aware of any precedent studies using the proposed end-of-life design, so it is difficult to make accurate predictions on enrollment rates, follow-up rates and autopsy percentages.

Other Potential Reference Standards

Reference standards other than histopathological detection of amyloid plaques post-mortem have been considered. They included serological markers, cerebrospinal fluid (CSF) markers, and imaging methods. These markers, their advantages and disadvantages are summarized in Table 6, below.

Table 6. Reference standards other than histopathology.

<u>Method</u>	<u>Strengths</u>	<u>Weaknesses</u>
Clinical assessment	Widely available and utilized	Low specificity No spatial information
Clinical follow-up (e.g. repeat diagnostic evaluation after 1 year)	Widely available and utilized	No evidence that follow-up diagnosis is more accurate than initial diagnosis
CSF or blood biomarkers	Good research data available CSF markers track amyloid and tau peptides	Still in research stage Overlap between groups; high variability No spatial information
MRI volumetric measurements	Good research data available High spatial resolution Spatial information on atrophy	Still in research stage Small differences Not AD specific
¹⁸ F-FDG PET	Good research data available Spatial information on hypometabolism	Does not measure primary pathology Not AD specific
¹¹ C-PiB PET	Good research data available Establishes potential of amyloid PET imaging	Still in research stage Non-IND studies & drug not approved Very short half-life of ¹¹ C limits use to expert centers
<i>Histopathology</i>	Defining pathology Widely accepted & endorsed Spatial correlation possible High precision measure	Technical challenges require novel trial designs to ensure feasibility

Of the reference standards listed, only post-mortem histopathological detection of amyloid plaques determines a defining feature of AD. In addition, none of the other reference standards has obtained regulatory approval for the diagnosis of AD.

d. Supportive Clinical Trials

Avid is also conducting several other studies which will enroll ~500 well-characterized subjects, both cognitively normal individuals as well as those with AD, MCI, or FTD (frontal-temporal dementia). Avid expects that these trials will provide substantial data on the safety of ¹⁸F-AV-45, as well as demonstrate: 1) a high positive PET scan rate (based on blinded reader assessment) for the population having a high prevalence of amyloid plaque pathology (AD subjects), 2) a high negative PET scan rate for the population having a low prevalence of amyloid plaque pathology (normal control and FTD subjects), and 3) intermediate positive and negative PET scan rates for the population with intermediate prevalence of amyloid plaque.

The A05 trial will evaluate ¹⁸F-AV-45 PET in 180 subjects, including healthy controls, subjects with MCI and subjects with AD. The -A08 trial will study ¹⁸F-AV-45 PET in up to 50 subjects, including healthy controls, and subjects with FTD or AD-based dementias. The A06 trial is an “all-comers” study designed to show that in the target population of cognitively impaired subjects presenting for neurological evaluation, the ¹⁸F-AV-45 PET scan gives the expected high NPV (i.e. negative scan rate) in subjects receiving a diagnosis consistent with a low probability of Aβ pathology (not-AD population) and the expected high PPV (i.e. positive scan rate) in subjects receiving a diagnosis consistent with a high probability of Aβ pathology (probable AD population). This A06 study will enroll approximately 150 subjects presenting for initial diagnostic work-up of cognitive impairment. An expert (physician) assessment will be used as a reference standard for amyloid status (using all available clinical, imaging and biomarker data (except the ¹⁸F-AV-45 PET scan results). However, the reference standard of clinical diagnosis of probable AD only has a specificity of 70% and sensitivity of 81% for detecting definite AD (as determined at autopsy; Knoppman et al, 2001). This means that any estimation of sensitivity and specificity of ¹⁸F-AV-45 for amyloid plaque detection will be significantly distorted by clinical diagnostic errors. In order to mitigate this problem we will establish sensitivity for detection of amyloid plaques using only patients who based on clinical expert diagnosticians are thought to have a very high probability of having AD (and thus being amyloid plaque positive). Similarly we will establish specificity by studying patients who have a very low likelihood for having amyloid plaques (e.g. elderly subjects with other known causes of dementia; in addition it may be necessary to supplement with young healthy subjects in order to increase the number of high probability amyloid negative subjects). In many patients presenting for diagnosis (e.g. MCI patients, possible AD diagnoses, patients meeting criteria for multiple diagnoses) the reference standard diagnosis will be too uncertain for use in validating ¹⁸F-AV-45. Data on these subjects will be collected and evaluated in secondary analyses.

e. Overview of Proposed Phase III Histopathology Trial (Autopsy Study)¹⁸F-AV-45-A07: Correlation of PET imaging of amyloid plaque with post-mortem histopathology

The ¹⁸F-AV-45-A07 study will evaluate the efficacy of ¹⁸F-AV-45 PET imaging as a biomarker test for the presence or absence of clinically significant amyloid plaque pathology. This study is being carried out to test the hypothesis that ¹⁸F-AV-45 PET imaging is highly correlated to post-mortem histopathological measurement of amyloid plaque as determined by CERAD criteria. This trial is designed as a Phase II / III trial and a synopsis is provided in the following section 8. Approximately 75 subjects with terminal medical conditions (anticipated life expectancy ≤ 6 months as determined by the principal investigator) will be enrolled in this trial. The sample size may be adjusted based on the results of the first 10 patients in the Phase II portion of this two part (Phase II/III) trial.

8. SYNOPSIS OF PROPOSED PHASE III HISTOPATHOLOGY CORRELATION TRIAL (AUTOPSY STUDY)

¹⁸F-AV-45 is under development for the proposed indication: *¹⁸F-AV-45 is indicated for PET imaging of amyloid plaque pathology in the brain to aid in the evaluation of patients with signs or symptoms of cognitive impairment.* The –A07 histopathology correlation trial described in this section is designed to demonstrate that ¹⁸F-AV-45 is a safe and effective marker for evaluating amyloid plaque pathology in the brain. This trial is based on the comparison of ¹⁸F-AV-45 PET imaging to post-mortem histopathology as the reference standard (“standard of truth”) for the presence/absence of amyloid plaque pathology. In this histopathology reference standard trial, ¹⁸F-AV-45-A07 (synopsis below), we have selected the best available truth standard (neuritic amyloid plaque burden assessed by CERAD criteria) for defining the presence or absence of amyloid plaque pathology.

In this study the goal is to demonstrate efficacy for evaluating amyloid plaque pathology by comparing imaging results to autopsy confirmation of plaque pathology (i.e. the reference standard) in terminally ill subjects. A protocol synopsis for this Phase II/III trial, ¹⁸F-AV-45-A07, is provided below.

Sponsor: Avid Radiopharmaceuticals, Inc.	Name of Compound: ¹⁸ F-AV-45 Injection	Active Ingredient(s): ¹⁸ F-AV-45 (E)-4-(2-(6-(2-(2-(2-[¹⁸ F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N- methylbenzenamine
Title of Study: A Two-Part Front-running Phase II/III Study of the Correspondence Between ¹⁸ F-AV-45 PET Imaging and Post-Mortem Amyloid Plaque Pathology.		
Test Product: ¹⁸ F-AV-45 Dose: 370 MBq (10 mCi) Route of Administration: Intravenous (i.v.)		
Study Phase: II/III		
Study Centers: Up to 10 centers		
Planned number of subjects: Approximately 75 subjects may be enrolled and imaged with ¹⁸ F-AV-45 PET in order to obtain the required number of post mortem histological evaluations on patients coming to autopsy within one year of PET imaging. The sample size may be adjusted based on the results of the first 10 patients in the Phase II portion of this two part (Phase II/III) front-running design.		

Sponsor: Avid Radiopharmaceuticals, Inc.	Name of Compound: ¹⁸ F-AV-45 Injection	Active Ingredient(s): ¹⁸ F-AV-45 (E)-4-(2-(6-(2-(2-(2-[¹⁸ F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N- methylbenzenamine
<p>Primary Aim</p> <ol style="list-style-type: none"> Determine whether subjects rated as having a low amyloid burden (Aβ negative: not Alzheimer’s disease-like) as determined by ¹⁸F-AV-45 Positron Emission Tomography (PET) imaging show low levels of neuritic amyloid plaques (Consortium to Establish a Registry for Alzheimer’s Disease [CERAD] none or sparse) upon post-mortem histopathological evaluation. <ol style="list-style-type: none"> <i>Hypothesis 1:</i> Low ¹⁸F-AV-45 retention in PET imaging of neocortical regions is associated with low neocortical neuritic plaque on neuropathological examination. <p>Secondary Aims</p> <ol style="list-style-type: none"> Determine the relationship between amyloid burden as determined by ¹⁸F-AV-45 PET imaging and amyloid deposition as defined on histopathology by neuritic plaques, diffuse plaques and amyloid angiopathy. <ol style="list-style-type: none"> <i>Hypothesis 1:</i> Subjects rated as Aβ positive/AD-like on PET scan will have greater amyloid deposition on neuropathological evaluation than subjects rated as Aβ negative on PET scan. Correlate regional ¹⁸F-AV-45 cortical uptake as determined by ¹⁸F-AV-45 PET imaging to neuritic amyloid plaque counts in corresponding brain regions on autopsy. <ol style="list-style-type: none"> <i>Hypothesis 1:</i> When evaluated across regions within individual subjects, regions with the highest plaque counts will tend to have the highest levels of ¹⁸F-AV-45 retention on the PET image. <i>Hypothesis 2:</i> When evaluated across subjects, plaque counts in various target regions (individual Volumes of Interest – VOIs - and neocortical mean VOI) will correlate with ¹⁸F-AV-45 retention in those same regions on the PET image (i.e., subjects with the highest plaque counts in a particular region will tend to show the highest levels of ¹⁸F-AV-45 retention in that same region). Determine the relationship between ¹⁸F-AV-45 retention as determined by PET imaging and the neuropathologically determined likelihood that AD is present using Reagan criteria. <ol style="list-style-type: none"> <i>Hypothesis 1:</i> There will be a trend toward increasing probability of subjects being rated as having a high amyloid burden (Aβ positive; AD-like), based on ¹⁸F-AV-45 retention in neocortex, as neuropathological diagnosis changes from low likelihood to intermediate likelihood to high likelihood of dementia due to AD using Reagan criteria. <i>Hypothesis 2:</i> There will be a significant difference in ¹⁸F-AV-45 cortex to cerebellum SUVR values obtained from the PET image among subjects with neuropathological diagnosis of low likelihood, intermediate likelihood and high 		

Sponsor: Avid Radiopharmaceuticals, Inc.	Name of Compound: ¹⁸ F-AV-45 Injection	Active Ingredient(s): ¹⁸ F-AV-45 (<i>E</i>)-4-(2-(6-(2-(2-(2-[¹⁸ F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)- <i>N</i> -methylbenzenamine
likelihood of dementia due to AD using Reagan criteria.		
<p>Eligibility:</p> <p><u>Subjects may be enrolled if they:</u></p> <ul style="list-style-type: none"> • Are males or females ≥ 50 years of age; • Have a projected life expectancy of ≤ 6 months as determined by the principal investigator (terminal medical condition such as end-stage congestive heart failure, end-stage chronic obstructive pulmonary disease [COPD], end-stage renal disease, or end-stage cancer); • Can tolerate a 10 minute PET scan. The principal investigator will carefully assess each patient and use sound medical judgment to determine whether the patient can tolerate the PET scan procedure; • Give informed consent for study procedures and brain donation consistent with the legal requirements of the State in which they die; • Approximately one-third of subjects should meet NINCDS criteria for Alzheimer's disease (AD) (McKhann, 1984) or (Petersen, 2001) criteria for Mild Cognitive Impairment (MCI). <p><u>Subjects may not be enrolled if they:</u></p> <ul style="list-style-type: none"> • Have primary brain tumor, known metastases to the brain, central nervous system (CNS) lymphoma; • Have any major, focal structural loss of brain matter; • Are aggressively being treated with life sustaining measures (e.g., receiving chemotherapy, currently on respirator); • Have a clinically significant infectious disease, including Acquired Immune Deficiency Syndrome (AIDS), Human Immunodeficiency Virus (HIV) infection, previous positive test for hepatitis or HIV or Creutzfeldt-Jakob disease (CJD); • Are receiving any investigational medications, or have participated in a trial with investigational medications within the last 30 days; • Have ever participated in an experimental study with an amyloid targeting agent (e.g., immunotherapy, secretase inhibitor); • Have had a radiopharmaceutical imaging or treatment procedure within 7 days prior to the study imaging session (Imaging Day 1). 		
<p>Study Design:</p> <p>This study is designed to test the relationship between the absence or presence of neuritic amyloid plaques levels, as assessed by ¹⁸F-AV-45 PET imaging, and neuritic amyloid plaque burden as assessed by histology at autopsy. Approximately 75 subjects with terminal medical conditions (anticipated life expectancy ≤ 6 months as determined by the principal</p>		

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<p>investigator) will be enrolled in this trial. It is intended that approximately one-third (33%) of the subjects enrolled should have a diagnosis of AD or MCI. Screening assessments may take place over several days and will include collection of demographic information, diagnostic interview, and safety assessments. At the time of screening, subjects or caregivers will be asked to provide consent for participation in a local brain donation program if they have not already done so, in addition to providing informed consent for the screening and imaging procedures in the study.</p> <p>Subjects who qualify for the study will have a catheter(s) placed for intravenous (i.v.) administration of ¹⁸F-AV-45. Subjects will receive a single i.v. bolus of 10 mCi of ¹⁸F-AV-45 followed by brain PET imaging for 10 minutes duration, beginning approximately 50 minutes post-injection. Vital signs and safety labs will be obtained prior to the administration of ¹⁸F-AV-45 and at the completion of the imaging session. Adverse events will be continuously monitored during the imaging session. Subjects who experience an adverse event will not be discharged until the event has been resolved or stabilized.</p> <p>Neuropathological assessment will minimally follow the CERAD guidelines. Sections from CERAD specified neocortical regions of brain (superior-middle temporal gyrus, middle frontal gyrus, inferior parietal lobule, and anterior cingulate gyrus) and additional regions of interest described below will be sampled and embedded in paraffin. Sections will be stained with thioflavin-S and frequency of neuritic amyloid plaques will be evaluated semi-quantitatively (none, sparse, moderate or frequent) and quantitatively, as number of neuritic amyloid plaques per high powered field. A technical autopsy manual (TAM) will be developed for this study containing all methods and measurement procedures. All neuropathological measurements on brain tissue from subjects entered in this trial will be evaluated in a blinded fashion (with respect to PET image results) in a suitably qualified laboratory.</p> <p>The primary analysis will determine the correspondence between the classification of over-all low cortical amyloid burden by ¹⁸F-AV-45 PET imaging (Aβ-) and autopsy evaluation of over-all plaque burden (none/sparse). The primary analysis will focus on patients who come to autopsy within 12 months of PET imaging, because the link between the imaging data and the autopsy result may be less certain as neurodegeneration continues over time. Secondary analyses will determine the degree of correlation between regional plaque burden as measured by imaging (both qualitative image interpretation and quantitative image analysis using cortical to cerebellar SUVR [Standard Uptake Value Ratio]) and by pathology (semi-quantitative and quantitative amyloid plaque assessments).</p>		

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<p>Assessments and Endpoints:</p> <p>Screening assessments for all subjects will include:</p> <ul style="list-style-type: none"> • Informed consent (for clinical, imaging and autopsy procedures); • Demographics (age, gender, education); • Medical history, brief physical and neurological exam, concomitant medications; • Alzheimer's disease history (if relevant: duration/months since symptom onset, date/months since diagnosis, family history of neurologic disease); • Brief assessments will be made in the major domains impaired in AD by evaluating performance using standardized and validated tests assessing the domains of memory (CERAD list learning and delayed recall), language (animal verbal fluency), orientation (date), mental manipulation (WORLD backwards), and constructional praxis (clock draw); • Comprehensive interview with the patient's caregiver to include information about clinically meaningful decline in cognitive status during the past 5 years; • Safety (vital signs); and • A physician or appropriate designee evaluation and summary of current medical status. <p>The following assessments will be performed for all subjects on Imaging Day 1:</p> <ul style="list-style-type: none"> • The subject will be seen by the site physician who will assess their ability to safely tolerate the imaging procedure; • A 370 MBq (10 mCi) fast bolus injection of ¹⁸F-AV-45 will be administered intravenously and 10 minute continuous brain PET imaging will begin 50 minutes post-injection. A nuclear medicine physician or designee will reconstruct the image and review immediately after completion of the scan. If the investigator detects motion artifact or other technical failure, the scan will be repeated and the repeat scan will be used for study evaluation. An imaging technical operations manual (TOM) will be implemented at each study center and followed for image acquisition; • Vital signs and clinical safety labs will be taken immediately prior to administration of ¹⁸F-AV-45 (within 5 minutes prior to injection), and after completion of imaging, prior to discharge; • Subjects will be observed continuously for signs of adverse events (AE) or serious adverse events (SAE), all AEs and SAEs will be followed until resolution; • The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected; and • A physician will see the subject prior to discharge to evaluate the subject's readiness for discharge. 		

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<p>Follow-up for all enrolled subjects:</p> <ul style="list-style-type: none">Each study participant (or their caregiver if applicable) will be contacted by phone approximately 24-48 hours after they were injected with the investigational agent to confirm their well being and query them about any new adverse events. End of study for the purpose of adverse event reporting is defined as the time of the completion of the follow up telephone call.		
<p>Evaluation of Imaging:</p> <p>Images will be evaluated qualitatively and quantitatively. Images will be visually examined by three independent nuclear medicine specialists blinded to the clinical data and will be classified as Aβ+ (amyloid positive, AD-like) or Aβ- (amyloid negative, not AD). Regional assessments will also be made. Limited sequential unblinding may explore the value of additional information such as age and medical history. For quantitative evaluation, standard uptake values (SUVs) will be calculated for target areas drawn to correspond closely with the regions of interest for autopsy sampling. SUVR for cortical target areas relative to the cerebellum and centrum semiovale will be calculated. A global mean SUVR will also be calculated for both the CERAD cortical target areas (frontal cortex, temporal cortex, parietal cortex and anterior cingulate) and the expanded cortical target areas (frontal cortex, temporal cortex, parietal cortex and anterior cingulate, posterior cingulate and precuneus).</p> <p>Because this is the first study of its type, a two-part Phase II/III front-running design is proposed to allow the final Phase III image evaluation criteria to be modified based on results from the first few (up to 10) subjects to come to autopsy in the Phase II portion of the protocol. A preliminary methodology for qualitative and quantitative image evaluation will be documented before the study is initiated. Final image evaluation criteria, and sample size and statistical analyses plans, will be issued as charters before the first patient is evaluated in the Phase III portion of the protocol.</p>		
<p>Neuropathology Evaluation:</p> <p>Subjects will be consented to participate in a brain donation program. For those subjects who come to autopsy within 12 months, sections of brain from various anatomic regions will be sampled and embedded in paraffin. Sections will be stained with thioflavin-S as well as other histochemical and immunohistochemical techniques and a neuropathologist, blinded to the clinical history and imaging data, will evaluate the frequency of amyloid plaques of the neuritic type. Plaques will be scored using the semiquantitative CERAD rating system (none, sparse, moderate, or frequent).</p>		

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<p>The neuropathologist will assess the over-all amyloid plaque status for the patient using a forced choice:</p> <p>(A) None-sparse amyloid plaques, not consistent with AD <or></p> <p>(B) Moderate-frequent amyloid plaques, consistent with AD</p> <p>The neuropathologist will assess the burden of neurofibrillary tangles and other pathologies using histochemical and immunohistochemical techniques and a neuropathological diagnosis will be made.</p> <p>The neuropathologist reader will then be unblinded to clinical history and a final neuropathological diagnosis (taking into account the neuropathology findings and the clinical history) will be made.</p>		
<p>Statistical Methods:</p> <p>The primary analysis will determine the proportion of subjects with a low neuritic amyloid burden (Aβ-, not AD-like) as determined by ¹⁸F-AV-45 PET imaging that have low levels of amyloid (CERAD none or sparse) upon autopsy evaluation. The denominator will be the number of subjects with a low neuritic amyloid burden (Aβ-, not AD-like) as determined by the blinded read of ¹⁸F-AV-45 PET imaging. The proportion and percentage as well as the 95% confidence interval will be presented.</p> <p>The ratio of SUV (SUVR) relative to cerebellar cortex and relative to centrum semiovale will be determined. Descriptive statistics (n, mean, SD, median, minimum and maximum values) will be summarized for SUVR and neuritic amyloid plaque burden counts by brain region. Secondary analyses will evaluate the correlation between neuritic amyloid plaque burden as assessed by counts per high powered field upon autopsy evaluation and neuritic amyloid plaque burden as assessed by ¹⁸F-AV-45 PET imaging (SUVR in the corresponding cortical target areas).</p> <p>Additional analyses will determine whether degree of neocortical ¹⁸F-AV-45 retention corresponds with neuropathological diagnosis of AD (low likelihood, intermediate likelihood or high likelihood that the dementia is due to AD) using Reagan criteria. A 2 x 3 table will be generated with number and percentages reported for each cell. A Cochran-Armitage test for trend will be determined across the three ordinal categories of the Reagan criteria. Additionally, the SUVR will be summarized as a function of Reagan criterion category.</p>		

Analyses of variance will compare SUVR across categories.

Because this study is the first of its kind, because there is an extended follow-up period after enrollment and because there is an urgent need to develop new diagnostic methods for Alzheimer's disease, a two-part front-running design will be employed. For the purposes of analysis, the study will be divided into two parts. During the first (Phase II) part of the protocol, which can last for up to 10 subjects, image evaluation is performed as the subject comes to autopsy. At any point during this phase, but not later than completion of the 10th autopsy, the final Phase III methods and sample size will be specified, and no further modifications to the image evaluation procedures will be allowed. All remaining images will then be evaluated, with all results at that point considered final.

The primary Phase III efficacy population for the purposes of this study will then be those subjects whose images were read and who come to autopsy after the final image evaluation plan is determined. However, secondary analyses will also be performed including all patients, with the first 10 subjects considered both based on the initial image interpretation and the interpretation under the revised image evaluation guideline.

9. PROPOSED POST-NDA STUDIES AND DATA COLLECTION

a. PHASE IIIb AND PHASE IV TRIALS

Avid proposes to do additional well-controlled studies as Phase IIIb trials during and beyond the initial NDA submission. These will include studies to examine the utility of ¹⁸F-AV-45 PET for risk stratification/prognosis in patients at risk for progressing to AD (e.g. MCI). Preliminary estimates by Avid suggest that the risk-stratification and prognostic trials will enroll approximately 250-300 MCI subjects (mixed amnesic and non-amnesic) and will require approximately 3 years of follow-up to monitor the rate of progression and rate of conversion to a clinical diagnosis of AD.

Avid also plans to extend current ¹⁸F-AV-45 PET studies being conducted in subjects receiving new experimental amyloid plaque-targeted drugs to Phase IIIb-designed studies. The goal of these studies would be to identify PET image characteristics which separate responders from non-responders to plaque-lowering or plaque-inhibiting drugs.

b. REGISTRY DATABASE

Following initial NDA approval Avid will work with the FDA Office of Surveillance & Epidemiology, and professional societies and patient advocacy organizations to establish a registry of patient data containing ¹⁸F-AV-45 PET images. By this mechanism long term (5-10 year) studies and follow-up data will be generated. This, in turn, is expected to lead to further insight into the role of early amyloid plaque deposition in the brain with regards to the epidemiology and risk factors associated with Alzheimer's disease.

10. REFERENCES

- American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. American Psychiatric Association: Washington, DC, 1994.
- Brunnstrom H, Gustafson L, Passant U, Englund E, Prevalence of dementia subtypes: A 30-year retrospective survey of neuropathological reports. *Arch. Gerontol. Geriatr.* Aug 7 2008.
- Jagust WJ, Zheng L, Harvey DJ, et al. Neuropathological basis of magnetic resonance images in aging and dementia. *Ann. Neurol.* 63(1): 72-80, 2008.
- Jagust WJ, Reed B, Mungas D, et al. What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? *Neurology*, 69:871-877, 2007.
- Jellinger K, Danielczyk W, Fischer P, Gabriel E. Clinicopathological analysis of dementia disorders in the elderly. *J. Neurol. Sci.* 95(3): 239-258, 1990.
- Klunk WE, Wang Y, Huang G, et al. Uncharged thioflavin-T derivatives bind to amyloid-beta protein with high affinity and readily enter the brain. *Life Sciences* 69:1471-1484, 2001.
- Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol.* 55:306-319, 2004.
- Klunk WE, Lopresti BJ, Ikonovic MD, et al. Binding of the positron emission tomography tracer Pittsburgh compound-B reflects the amount of amyloid-beta in Alzheimer's disease brain but not in transgenic mouse brain. *J Neurosci.* 25:10598-606, 2005.
- Klunk WE, Wang Y, Huang G, et al. Uncharged thioflavin-T derivatives bind to amyloid-beta protein with high affinity and readily enter the brain. *Life Sciences* 69: 1471-1484, 2001.
- Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: Diagnosis of dementia (An evidence-based review). *Neurology*, 56:1143-1153, 2001.
- Lopponen, M., Raiha, I., Isoaho, R., et al. Diagnosing impairment and dementia in primary health care-a more active approach is needed. *Age Aging*, 32:606-612, 2003.
- Lopresti BJ, Klunk WE, Mathis CA, et al. Simplified quantification of Pittsburgh Compound B amyloid imaging PET studies: a comparative analysis. *J Nucl Med.* 46:1959-1972, 2005.
- McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34: 939-944, 1984.
- Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology*, 41:479-86, 1991.
- Petersen, R.C., Stevens, J.C., Ganguli, M., et al. Practice Parameter: Early detection of dementia: Mild cognitive impairment (an evidence based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology, 56:1133-1152, 2001.
- Silverman DH, Small GW, Chang CY, et al. Positron emission tomography in evaluation of dementia: Regional brain metabolism and long-term outcome. *JAMA.* 286:2120-2127, 2001.

- Solomon, P.R., Brush, M., Calvo, V., et al. Identifying dementia in the primary care practice. *International Psychogeriatrics*, 12:483-493, 2000.
- Thal LJ, Kantarci K, Reiman EM, et al. The Role of Biomarkers in Clinical Trials for Alzheimer Disease. *Alzheimer's Disease and Associated Disorders*, 20: 6–15, 2006.
- Victoroff J, Mack WJ, Lyness SA, Chui HC, Multicenter Clinicopathological Correlation in Dementia, *A. J. Psychiatry* 152: 1476-1484, 1995.
- Walker Z, Jaros E, walker RW, et al., Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. *J. Neurol. Neurosurg. Psychiatry*. 78(11): 1176-1181, 2007.
- Zhang W, Kung MP, Oya, S, Hou C, Kung, MP. ¹⁸F-labeled styrylpyridines as PET agents for amyloid plaque imaging. *Nucl. Med. Biol.* 34: 89-97, 2007.