**Protocol Number:** **$^{18}$F-AV-45-A14**

**Date and Version:** **February 1, 2013 - Amendment #3**

**Test Agent:** **Florbetapir F 18 ($^{18}$F-AV-45) Injection**

**Title:** **Clinical Evaluation of Florbetapir F 18 ($^{18}$F-AV-45)**

**IND Sponsor:** **Avid Radiopharmaceuticals, Inc.**

**Approvals/Signatures:**

Mark A. Mintun, M.D
Chief Medical Officer

04 Feb 2013
Date

**CONFIDENTIAL**

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

**Title of Protocol:** $^{18}$F-AV-45-A14

Clinical Evaluation of Florbetapir F 18 ($^{18}$F-AV-45)

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

**Dose:** 370 MBq (10 mCi)

**Route of Administration:** Intravenous ( i.v.) bolus

**Study Phase:** II

**Study Centers:** Approximately 40

**Objectives:**

This protocol is designed to standardize imaging studies using florbetapir F 18 PET to provide information on amyloid burden in subjects participating in other studies (companion protocol) such as longitudinal studies of aging and studies of biomarkers for neurodegenerative diseases.

The primary objectives of this protocol are to:

- expand the database of florbetapir F 18 safety, amyloid binding as measured by PET imaging, and long-term outcome in cognitively normal volunteers, patients with AD, patients with MCI, and patients with other neurodegenerative diseases; and
- provide standardized conditions for florbetapir F 18 use, data collection and analysis to facilitate evaluation of subject's amyloid burden in companion studies including, but not limited to, longitudinal studies of aging, studies of progressive cognitive impairment and studies of imaging and blood/CSF biomarkers of neurodegenerative disease.

**Planned number of subjects to be enrolled:**

Approximately 1,800 subjects, including cognitively healthy controls, subjects with mild cognitive impairment (MCI) and patients with Alzheimer's disease (AD), will be enrolled in the study. With prior discussion and consent of the sponsor, investigators may also be permitted to enroll subjects with other disorders such as Parkinson's disease, Frontal-temporal dementia, traumatic brain injury or vascular dementia.

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**Eligibility:**

Subjects should meet inclusion and exclusion criteria for the companion protocol, and in addition:

Subjects who meet all of the following criteria are eligible to enroll in this study:

1. Male or female subjects at least 18 years of age;
2. Subjects who sign an IRB approved informed consent prior to any study procedures. Where subjects are deemed incapable of informed consent, a legally authorized representative may provide consent, with the subject's documented assent; and
3. Subjects who in the opinion of the investigator can tolerate the PET scan procedures.

Subjects will be excluded from enrollment if they:

1. Have clinically significant hepatic, renal, pulmonary, metabolic, or endocrine disturbances as indicated by history, which in the opinion of the investigator might pose a potential safety risk to the subject;
2. Have current clinically significant cardiovascular disease. Clinically significant cardiovascular disease usually includes one or more of the following:
   - cardiac surgery or myocardial infarction within the last 4 weeks;
   - unstable angina;
   - acute decompensated congestive heart failure or class IV heart failure;
   - current significant cardiac arrhythmia or conduction disturbance, particularly those resulting in ventricular fibrillation, or causing syncope, or near syncope;
   - uncontrolled high blood pressure; or
   - QTc > 450 msec (by history or for patients with cardiac disease by screening evaluation in companion study)

   Before enrolling a patient with any of the above conditions, the investigator must have performed a cardiac evaluation and obtain permission from the sponsor.
3. Have a history of drug or alcohol abuse within the last year, or prior prolonged history of abuse;
4. Women of childbearing potential who are not surgically sterile, not refraining from sexual activity or not using reliable methods of contraception. Women of childbearing potential must not be pregnant (negative urine beta-hCG at the time of screening and negative urine beta-hCG on the day of imaging) or breastfeeding at screening. Women must avoid becoming pregnant, and must agree to refrain from sexual activity or to use reliable contraceptive methods for 24 hours following administration of Florbetapir F 18 Injection ( such as oral contraceptives for at least three months or an IUD for at least two months prior to the start of the screening visit, or various barrier methods, e.g., diaphragm or combination condom and spermicide);

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5. Have a history of relevant severe drug allergy or hypersensitivity (Relevant severe drug allergies should be determined by the PI, and any questions about a subject's eligibility can be directed to Avid. If a subject has a history of severe drug allergies, it may be dangerous for them to participate in a study);
6. Are patients who have received an investigational medication under an FDA IND protocol within the last 30 days. Additionally, the time between the last dose of the previous experimental medication and enrollment (completion of screening assessments) must be at least equal to 5 times the terminal half-life of the previous experimental medication. Patients who have ever participated in an experimental study with an amyloid targeting therapy (e.g., immunotherapy, secretase inhibitor) may not be enrolled without prior sponsor approval unless it can be demonstrated that the patient received only placebo in the course of the trial;
7. Are patients with current clinically significant unstable medical comorbidities, as indicated by history or physical exam that pose a potential safety risk to the subject.
8. Are patients who have received a radiopharmaceutical for imaging or therapy within the past 24 hours prior to the imaging session for this study. If another radiotracer is required in the companion protocol, patients may be able to receive a radiopharmaceutical for imaging or therapy within the 24 hours prior to the imaging session with prior sponsor approval and at the discretion of the investigator; and
9. Are patients who, in the opinion of the investigator, are otherwise unsuitable for a study of this type.

If at the time of enrollment subjects do not meet all eligibility criteria, the subjects may still be enrolled if documentation is provided demonstrating that the subject will meet all criteria at the time of the first imaging procedure.

**Study Design:**

Study $^{18}$F-AV-45-A14 is designed to expand the database of florbetapir F 18 safety and amyloid binding as measured by PET imaging, and to provide standardized conditions for florbetapir F 18 use, data collection and analysis to facilitate companion studies including, but not limited to, longitudinal studies of aging, studies of progressive cognitive impairment and studies of imaging and blood/CSF biomarkers of neurodegenerative disease. Approximately 1,800 subjects will be studied under this protocol.

Screening assessments may take place over several days and will include collection of demographic information, a medical assessment for eligibility, and a brief cognitive assessment, including an MMSE. Investigators will be encouraged, but not required, as part of their companion studies, to collect certain common data, such as Uniform Data Set cognitive assessments and MRI scans according to the Alzheimer's Disease Neuroimaging Initiative protocol, to facilitate potential pooling of data by and among investigators.

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Subjects who qualify for the study will come to the imaging center at a later date and will have a catheter(s) placed for i.v. administration of Florbetapir F 18 ($^{18}$F-AV-45) Injection. Vital signs will be taken in a supine position immediately prior to administration of florbetapir F 18 (within 30 minutes prior to injection). Subjects will receive a single i.v. bolus of florbetapir F 18, followed by brain PET imaging of 10 minutes duration, approximately 50 minutes post-dose injection. Sites with dynamic PET acquisition capabilities may elect to acquire a 20 minute acquisition, beginning 30 to 50 minutes post injection. If a 20 minute acquisition is chosen, the site will reconstruct at least one 10 minute image from the dataset in addition to a 20 minute reconstruction. All datasets will be submitted to the sponsor for analysis. Sites may elect additional imaging timepoints with prior approval from the sponsor.

Adverse events will be continuously monitored during the imaging session. Subjects who experience any adverse event will not be discharged until the event has resolved or stabilized. A follow-up phone call to the patient (or the caregiver as applicable) will be conducted 24-72 hours after the imaging session to confirm patient well-being and to collect information about any new adverse events that may have occurred within 24 hours post-injection.

With prior sponsor approval and at the discretion of the investigator, a subgroup of not more than 5 subjects will be given the option of having a regimen of arterial blood sampling with up to 70 minutes of imaging beginning immediately after florbetapir F 18 administration.

A separate subgroup of subjects, with prior sponsor approval and at the discretion of the investigator may have up to two imaging sessions within a 12 month timeframe.

Images will be evaluated qualitatively and/or quantitatively. For qualitative evaluation, images will be visually examined and will be classified as Aß+ (amyloid positive) or Aß- (amyloid negative). For quantitative evaluation, standard uptake values (SUV) will be calculated for cortical target areas (frontal cortex, temporal cortex, parietal cortex, precuneus, anterior and posterior cingulate) and the cerebellum. SUV ratios (SUVR) for cortical target areas relative to the cerebellum will also be calculated and a global mean SUVR will be calculated from the average across all cortical target areas.

**Assessments and Endpoints:**

***Screening Day:***

Screening may take place over several days. All screening assessments will preferably be performed within 30 days prior to the PET imaging session. Some screening assessments may be performed on imaging day prior to injection with sponsor approval. Screening assessments will include:

- Informed consent;

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- Demographics (age, gender, education, race, ethnicity);
- Medical history, concomitant medications;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of relevant neurologic disease);
- Cognitive status interview, including MMSE;
- Where appropriate, informant interview with family member or close friend who is familiar with subject's everyday functioning abilities;
- Urine pregnancy test (women of childbearing potential); and
- A physician will see the patient during the screening visit.

Demographic information, cognitive status assessment or MMSE collected within the last 30 days as part of a companion protocol or clinic visit need not be repeated.

***Imaging Day:***

The following assessments will be performed for all subjects:

- Females of childbearing potential will have a urine pregnancy dipstick test prior to injection (the result must be negative for the subject to be administered florbetapir F 18);
- Vital signs will be taken in a supine position immediately prior to administration of florbetapir F 18 (within 30 minutes prior to injection). Body weight will be measured with the subject lightly clothed;
- A 370 MBq bolus injection of florbetapir F 18 will be administered and a 10-minute continuous brain PET imaging scan will begin approximately 50 minutes post-injection. Sites with dynamic PET acquisition capabilities may elect to acquire a 20 minute acquisition, beginning 30 to 50 minutes post injection. If a 20 minute acquisition is chosen, the site will reconstruct at least one 10 minute image from the dataset in addition to a 20 minute reconstruction. All datasets will be submitted to the sponsor for analysis. Sites may elect additional imaging timepoints with prior approval from the sponsor.
- PET acquisitions will be reconstructed immediately after scanning is complete, and if any motion is detected, another continuous scan will be acquired. With prior sponsor approval and at the discretion of the investigator, a subgroup of not more than 5 subjects will be given the option of having a regimen of arterial blood sampling with up to 70 minutes of imaging beginning immediately after florbetapir F 18 administration. See Appendix 11.4 for detailed instructions on arterial blood sampling;
- Subjects will be observed continuously for signs of adverse events or serious adverse events;
- The injection site will be observed for excessive inflammation or damage to the

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surrounding tissue where the dose was injected; and

- A physician or physician designee will see the patient prior to dosing and prior to discharge.

***Follow-up:***

Each study participant will be contacted by phone 24-72 hours after they were injected with the investigational agent to confirm their well-being and query them about any new adverse events that may have occurred within 24 hours post-injection.

***Repeat imaging:***

Longitudinal imaging studies may be conducted under protocol $^{18}$F-AV-45-A14, with prior sponsor approval and at the discretion of the investigator. In these studies subjects may have up to two imaging sessions within a 12 month timeframe. Procedures for each day will be identical to those described above.

***Evaluation of Imaging:***

Images will be evaluated qualitatively and/or quantitatively:

- Images will be visually examined by a trained radiologist or nuclear medicine physician who is blinded to the subject diagnosis and will be reported as either Aβ positive or Aβ negative.

- SUV for target areas such as frontal cortex, temporal cortex, parietal cortex, posterior cingulate cortex, anterior cingulate and precuneus, and reference regions including cerebellum will be calculated. SUVR for cortical target areas relative to cerebellum will also be calculated.

**Statistical Methods:**

**General Statistical Considerations**

All values will be summarized by diagnostic groups. Generally, patients should be classified as Alzheimer's disease (AD), mild cognitive impairment (MCI) or cognitively healthy volunteers in accordance with the classification guidelines in Appendix 11.3. However, alternative criteria may be used if specified in the companion protocol. Frequency distributions including counts and percents will be included for all categorical outcomes. Summary statistics including mean, standard deviation, median, minimum and maximum values will be presented for all continuous outcomes.

**Populations for Analysis**

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The efficacy population will include all patients for whom image data are available. All analyses involving amyloid imaging outcomes will be based on the efficacy population. All subjects who receive florbetapir will be included in the safety population.

**Efficacy (Imaging Results)**

- Qualitative assessment of image (Aβ+ or Aβ-)
- Quantitative assessment (SUVR) associated with the following brain regions:
  Frontal cortex
  Temporal cortex
  Parietal cortex
  Posterior cingular cortex
  Anterior cingulate
  Precuneus
  Global average of all of the above

Summary statistics will be provided as indicated above.

**Demographic, Baseline Characteristics and Cognitive Scales**

Frequency distributions and summary statistics for demographic and baseline variables will be presented by diagnostic group and for all subjects combined. Key demographic and baseline characteristics to be summarized include, but are not limited to: age, gender, education, race, and disease history.

Summary statistics for MMSE will be presented by diagnostic group and overall.

**Safety Analysis**

The number and percentage of subjects who experience adverse events and serious adverse events will be summarized by diagnostic group and total population.

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# 1. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, affecting more than 4 million people in the United States alone. However, diagnosis and treatment of the disease have been hampered by the absence of reliable non-invasive markers for the underlying pathology. Although diagnosis based on consensus criteria (McKhann et al. 1984; American Psychiatric Association, DSM, 4th Edition, 1994) is reasonably accurate by comparison to the gold standard of pathology at autopsy, (Knopman et al. 2001; Jobst et al. 1998) approximately 10% of community dwelling elderly still have undiagnosed dementia (Solomon et al. 2000; Lopponen et al. 2003). Community physicians may fail to diagnose up to 33% of mild dementia cases (Lopponen et al. 2003). The medical system does not have the resources to routinely send all elderly subjects with memory complaints for comprehensive expert evaluation. Thus, there is a need for a diagnostic aid or biomarker that can help community physicians separate those patients who do not have AD from those who have pathological signs and should be referred for further evaluation.

A reliable biomarker might aid diagnosis by documenting the presence or absence of disease-related pathology. Additionally, a biomarker could be useful for early identification of subjects at risk for developing AD (Thal et al. 2006). The present study is designed to continue the evaluation of $^{18}$F-labeled positron emission tomography (PET) imaging agent, florbetapir F 18, that binds with high affinity to the amyloid-β (Aβ) peptide fibrils that constitute amyloid plaques, and thus, has the potential to be an imaging biomarker for amyloid deposits in subjects with cognitive impairment.

Although the etiology of AD has not been definitively established, converging evidence suggests that the Aβ peptide may play an important role in the pathogenesis of the disease. Accumulation of Aβ fibrils in the form of amyloid plaques is one of the hallmarks of the disease, and is a key component of the neuropathological criteria for autopsy-based confirmation of diagnosis (Mirra et al. 1991; Hyman and Trojanowski 1997). Most cases of AD are thought to occur sporadically, but rare familial mutations known to produce an autosomal dominant form of the disease all directly or indirectly increase production or accumulation of specific forms of Aβ peptide and lead to the formation of amyloid plaques (Hardy and Higgins 1992; Hardy and Selkoe 2002). Transgenic mice that express one or more of these mutant human genes develop amyloid plaques, and behavioral/cognitive deficits that are similar in some respects to those seen in AD (Hsiao 1998; Gotz et al. 2004; Hock et al. 2003). Finally, experimental treatments that reduce Aβ peptide production or increase the clearance of Aβ from amyloid plaques have been successful in reversing behavioral deficits in these mice, and some of these treatments are now being tested in patients with AD (Hock et al. 2003).

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 Aβ levels in plasma or cerebral spinal fluid, imaging techniques

utilizing radiolabeled PET tracers that bind to the aggregated Aβ peptides in amyloid plaques have the potential to directly assess relative brain amyloid plaque pathology. To date the most widely researched imaging approach has utilized the $^{11}$C-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). Preliminary studies show that higher levels of radioactivity can be imaged in the cortex of patients with AD than in the cortex of healthy controls, presumably reflecting the elevated accumulation of Aβ pathology and consequent binding of PIB in the cortex of patients with AD (Lopresti et al. 2005).

Despite these encouraging results, the short half-life (20 minutes) of the $^{11}$C isotope may limit the utility of $^{11}$C-PIB as a tool for community based diagnostic screening and therapeutic evaluation. In contrast, florbetapir F 18 is an amyloid binding agent (Zhang et al. 2005; Zhang et al. 2006) labeled with $^{18}$F. Since $^{18}$F has a radioactive half-life of 110 minutes, regional preparation and shipping of doses is possible, thereby reducing the cost and increasing the number of potential imaging centers.

Studies conducted to date suggest that florbetapir F 18 may label amyloid plaques in a manner similar to PIB, and may have the potential to serve as an agent for in-vivo imaging of Aβ pathology in humans with AD. Florbetapir F 18 exhibits high-affinity, specific binding to amyloid plaques with a $K_d$ of 3.1 nM. In-vitro autoradiography studies further confirm that when applied at tracer concentrations florbetapir F 18 labels Aβ amyloid plaques in sections from patients with pathologically confirmed AD. The non-radioactive version of florbetapir F 18 can be prepared at high concentrations and shows very low to no affinity for all other central nervous system and cardiovascular receptors tested, including the hERG potassium channel binding site.

The potential toxicity of florbetapir was tested in rats with single acute doses (up to 100x) and 28 days of repeated doses (up to 25x) of the maximum human dose (MHD) of 50 μg. No clinically relevant adverse effects were observed on behavior, gross pathology, or histology in either study. Thus, in both studies, the no observed adverse effect level (NOAEL) was at or above the highest dose level tested (100x MHD for acute, 25x MHD for repeat-dose, allometrically scaled). 14-Day and 28-day repeat-dose intravenous toxicity studies were performed in beagle dogs, and there were no significant adverse effects based on clinical observations, weight, gross pathology or histopathology at any dose studied (highest dose levels were 8.7x and 25xMHD, respectively, allometrically scaled). In each rat and dog toxicity study conducted, the NOAEL was determined to be equal or higher than the highest dose level tested.

Potential genetic toxicity has been tested in both in vitro and in vivo assays. Bacterial reverse mutation assay results showed positive responses in 2 out of 5 tested strains. The human peripheral lymphocyte chromosomal aberration assay showed no statistically significant test-article related increases in the percent of cells with structural aberrations after three hours of treatment, but a statistically significant positive result was seen after 22 hours of exposure. In the in vivo micronucleus assay, florbetapir F 18 produced no evidence of genotoxicity when administered at doses up

to the highest practically-achievable dose (83x MHD) for three consecutive days. The different results in the in-vitro bacterial mutation and chromosome aberration assays and the in-vivo micronucleus study are likely related to differences in the exposure conditions encountered by the target cells in the different tests systems. Florbetapir cleared rapidly in-vivo whereas the in-vitro experiments employ static, prolonged exposure of cells to the test article and/or metabolites.

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 florbetapir corresponding to 25, 50, and 100x MHD (allometrically scaled). No test article-related adverse cardiovascular or respiratory effects were observed. No biologically significant prolongation of QTc was observed in any animal on any study day.

To determine the possible effects of commonly used drugs and drug candidates on florbetapir F 18 binding to β-amyloid, an in vitro drug-drug interaction study was conducted using tissue binding assay and in vitro film autoradiography techniques. The studies showed that none of the drugs tested interfered with florbetapir F 18 binding to β-amyloid at therapeutically meaningful concentrations.

The florbetapir investigator's brochure contains a current summary of the florbetapir human experience. In brief, a total of 555 subjects were studied in completed studies, included in the NDA. In addition more than 3,500 subjects have been studied in ongoing studies under Avid IND and in therapeutic trials in which florbetapir served as a biomarker. Across these studies, florbetapir F 18 was well-tolerated, and showed an acceptable radiation dosimetry profile (effective dose 7.0 mSv) at the proposed injected dose level of 10 mCi (370 MBq). Florbetapir-PET correlated with amyloid levels on histopathology, clinical diagnosis, age, and ApoE genotype.

The present study is designed to provide standardized conditions for florbetapir F 18 use, data collection and analysis to facilitate such proposed studies.

## 2. TRIAL OBJECTIVES

This protocol is designed to standardize imaging studies using florbetapir F 18 PET to provide information on amyloid burden in subjects participating in other studies (companion protocol) such as longitudinal studies of aging and studies of biomarkers for neurodegenerative diseases.

The primary objectives of this protocol are to:

- expand the database of florbetapir F 18 safety, amyloid binding as measured by PET imaging, and long-term outcome in cognitively normal volunteers, patients with AD, patients with MCI, and patients with other neurodegenerative diseases; and

- provide standardized conditions for florbetapir F 18 use, data collection and analysis to facilitate evaluation of subject's amyloid burden in companion studies including but not limited to longitudinal studies of aging, studies of progressive cognitive impairment and studies of imaging and blood/CSF biomarkers of neurodegenerative disease.

## 3. SPONSOR, INVESTIGATOR(S) AND OTHER PARTICIPANTS

The IND for florbetapir F 18 ($^{18}$F-AV-45) is sponsored by:

Avid Radiopharmaceuticals, Inc.
3711 Market Street, 7th Floor
Philadelphia, PA 19104
Phone: 215-298-0700
Fax: 413-826-0416

The IND sponsor's contact is:

Michael J. Pontecorvo, Ph.D.
Vice President, Clinical Development
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The IND sponsor's safety monitor is:
Andrew Siderowf, M.D.
Medical Director
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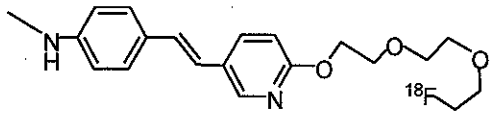
Fax: 413-826-0416
siderowf@avidrp.com

Approximately 40 centers may participate.

# 4. TEST DRUG AND CONTROL AGENTS

## 4.1 Descriptive Name: 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**
MW = 359.4 amu

## 4.2 Radioactive Labeling

The compound is labeled with [$^{18}$F] fluorine that decays by positron ($\beta^+$) emission and has a half life of 109.77 min. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron.

## 4.3 Decay Characteristics

The time course of radioactive decay for Fluorine [$^{18}$F] is shown below in Table 1.

| Minutes | Fraction Remaining |
|---|---|
| 0 | 1.000 |
| 30 | 0.827 |
| 60 | 0.685 |
| 90 | 0.567 |
| 120 | 0.469 |
| 150 | 0.388 |
| 180 | 0.321 |
| 210 | 0.266 |
| 240 | 0.220 |
| 270 | 0.182 |
| 300 | 0.150 |
| 330 | 0.125 |
| 360 | 0.103 |
| 390 | 0.085 |
| 420 | 0.071 |
| 450 | 0.058 |
| 480 | 0.048 |
| 510 | 0.040 |
| 540 | 0.033 |
| 570 | 0.027 |
| 600 | 0.023 |

Table 1: Physical decay chart for Fluorine [$^{18}$F]. Half-life = 109.77 min.

# 5. INVESTIGATIONAL PLAN

## 5.1 Overall Design and Plan of Trial

Protocol $^{18}$F-AV-45-A14 is designed to expand the database of florbetapir F 18 safety and amyloid binding as measured by PET imaging, and to provide standardized conditions for florbetapir F 18 use, data collection and analysis to facilitate companion studies including, but not limited to, longitudinal studies of aging, studies of progressive cognitive impairment and studies of imaging and blood/CSF biomarkers of neurodegenerative disease. Approximately 1,800 subjects will be studied under this protocol.

Screening assessments may take place over several days and will include collection of demographic information, a medical assessment for eligibility, and a brief cognitive interview, including an MMSE. Investigators will be encouraged, but not required, as part of their companion studies, to collect certain common data, such as Uniform Data Set cognitive assessments and MRI scans according to the Alzheimer's Disease Neuroimaging Initiative protocol, to facilitate potential pooling of data by and among investigators.

Subjects who qualify for the study will come to the imaging center at a later date and will have catheter(s) placed for i.v. administration of Florbetapir F 18 Injection. Vital signs will be taken in a supine position immediately prior to administration of florbetapir F 18 (within 30 minutes prior to injection). Subjects will receive a single i.v. bolus of florbetapir F 18, followed by brain PET imaging of 10 minutes duration, approximately 50 minutes post-dose injection. Sites with dynamic PET acquisition capabilities may elect to acquire a 20 minute acquisition, beginning 30 to 50 minutes post injection. If a 20 minute acquisition is chosen, the site will reconstruct at least one 10 minute image from the dataset in addition to a 20 minute reconstruction. All datasets will be submitted to the sponsor for analysis. Sites may elect additional imaging timepoints with prior approval from sponsor.

Adverse events will be continuously monitored during the imaging session. Subjects who experience any adverse event will not be discharged until the event has resolved or stabilized. A follow-up phone call to the patient (or the caregiver as applicable) will be conducted 24-72 hours after the imaging session to confirm patient well-being and to collect information about any new adverse events that may have occurred within 24 hours post-injection.

With prior sponsor approval and at the discretion of the investigator, a subgroup of not more than 5 subjects will be given the option of having a regimen of arterial blood sampling with up to 70 minutes of imaging beginning immediately after florbetapir F 18 administration. See Appendix 11.4 for detailed instructions on arterial blood sampling.

A separate subgroup of subjects, with prior sponsor approval and at the discretion of the investigator may have up to two imaging sessions within a 12 month

timeframe. Adverse events will not be collected during the time between the first follow-up phone call and the second imaging session.

Images will be evaluated qualitatively and/or quantitatively. For qualitative evaluation, images will be visually examined and will be classified as Aß+ (amyloid positive) or Aß- (amyloid negative). For quantitative evaluation, standard uptake values (SUV) will be calculated for cortical target areas (frontal cortex, temporal cortex, parietal cortex, precuneus, anterior and posterior cingulate) and the cerebellum. SUV ratios (SUVR) for cortical target areas relative to the cerebellum will also be calculated and a global mean SUVR will be calculated from the average across all cortical target areas.

## 5.2 Planned Dosage and Duration of Treatment

### 5.2.1 *Dosage and Administration*

During this protocol, subjects will receive a single i.v. administration of 370 MBq (10 mCi) of florbetapir F 18 (fast i.v. push) approximately 50 minutes prior to imaging. The injection of the imaging agent will be followed by a saline flush.

### 5.2.2 *Rationale for Dosage*

Based on data obtained in $^{18}$F-AV-45-A01, a 370 MBq (10 mCi) dose of florbetapir F 18 yielded excellent imaging results with reliable quantification. In study $^{18}$F-AV-45-A02, a 370 MBq dose showed acceptable human dosimetry (whole-body effective dose was approximately 7 mSv). Furthermore, in both clinical studies the agent was well tolerated, supporting the safety of the proposed dose. In addition, preclinical toxicology studies conducted at high multiples of the human mass dose support the safety of the proposed dose.

For these reasons a dose of 370 MBq (10 mCi) was chosen for the current study.

## 5.3 Selection of Subjects

Subjects should meet inclusion and exclusion criteria for the companion protocol, and in addition:

### 5.3.1 *Inclusion Criteria*

Subjects who meet all of the following criteria are eligible to enroll in this study:

1. Male or female subjects at least 18 years of age;

2. Subjects who sign an IRB approved informed consent prior to any study procedures. Where subjects are deemed incapable of informed consent, a legally authorized representative may provide consent, with the subject's documented assent; and
3. Subjects who in the opinion of the investigator can tolerate the PET scan procedures.

### 5.3.2 *Exclusion Criteria*

Subjects will be excluded from enrollment if they:

1. Have clinically significant hepatic, renal, pulmonary, metabolic, or endocrine disturbances as indicated by history, which in the opinion of the investigator might pose a potential safety risk to the subject;
2. Have current clinically significant cardiovascular disease. Clinically significant cardiovascular disease usually includes one or more of the following:
   - cardiac surgery or myocardial infarction within the last 4 weeks;
   - unstable angina;
   - acute decompensated congestive heart failure or class IV heart failure;
   - current significant cardiac arrhythmia or conduction disturbance, particularly those resulting in ventricular fibrillation, or causing syncope, or near syncope;
   - uncontrolled high blood pressure; or
   - QTc > 450 msec (by history or for patients with cardiac disease by screening evaluation in companion study)

   Before enrolling a patient with any of the above conditions, the investigator must have performed a cardiac evaluation and obtain permission from the sponsor.
3. Have a history of drug or alcohol abuse within the last year, or prior prolonged history of abuse;
4. Women of childbearing potential who are not surgically sterile, not refraining from sexual activity or not using reliable methods of contraception. Women of childbearing potential must not be pregnant (negative urine beta-hCG at the time of screening and negative urine beta-hCG on the day of imaging) or breastfeeding at screening. Women must avoid becoming pregnant, and must agree to refrain from sexual activity or to use reliable contraceptive methods for 24 hours following administration of Florbetapir F 18 Injection ( such as oral contraceptives for at least three months or an IUD for at least two months prior to the start of the screening visit, or various barrier methods, e.g., diaphragm or combination condom and spermicide);

5. Have a history of relevant severe drug allergy or hypersensitivity (Relevant severe drug allergies should be determined by the PI, and any questions about a subject's eligibility can be directed to Avid. If a subject has a history of severe drug allergies, it may be dangerous for them to participate in a study);
6. Are patients who have received an investigational medication under an FDA IND protocol within the last 30 days. Additionally, the time between the last dose of the previous experimental medication and enrollment (completion of screening assessments) must be at least equal to 5 times the terminal half-life of the previous experimental medication. Patients who have ever participated in an experimental study with an amyloid targeting therapy (e.g., immunotherapy, secretase inhibitor) may not be enrolled without prior sponsor approval unless it can be demonstrated that the patient received only placebo in the course of the trial;
7. Are patients with current clinically significant unstable medical comorbidities, as indicated by history or physical exam that pose a potential safety risk to the subject.
8. Are patients who have received a radiopharmaceutical for imaging or therapy within the past 24 hours prior to the imaging session for this study. If another radiotracer is required in the companion protocol, patients may be able to receive a radiopharmaceutical for imaging or therapy within the 24 hours prior to the imaging session with prior sponsor approval and at the discretion of the investigator; and
9. Are patients who, in the opinion of the investigator, are otherwise unsuitable for a study of this type.

If at the time of enrollment subjects do not meet all eligibility criteria, the subjects may still be enrolled if documentation is provided demonstrating that the subject will meet all criteria at the time of the first imaging procedure.

## 5.4 Prior and Concomitant Therapy

Except as noted below, all medications (prescription or OTC) that have been started prior to screening may be continued during the course of the trial. Attempts should be made to keep the dosage and administration stable throughout the trial (from screening through the end of the imaging session). Stable is generally defined as 2 weeks on therapy. All medications that are continued from the start of the trial or that are started during the trial (other than the study medication) must be documented on the Concomitant Medication Page of the Case Report Form (CRF).

- Patients with AD may be on a stable dose of an anticholinesterase and/or Namenda, and may be taking vitamin E at the time of imaging.

- Other treatments for dementia (i.e., off label prescription medications or nutracueticals) are discouraged.

- Investigators should carefully consider whether subjects requiring psychotropic medications for behavioral control will be able to complete the imaging session and necessary procedures such as cognitive testing.

Prohibited Medications:

- Patients who have ever participated in an experimental study with an amyloid targeting therapy (e.g., immunotherapy, secretase inhibitor, selective amyloid lowering agents) must not be enrolled without prior sponsor consent unless it can be demonstrated that the patient received only placebo in the course of the trial.

## 5.5 Removal of Subjects from Trial

Patients must be removed from the trial if:

1. Informed consent is withdrawn; or
2. The investigator or the sponsor believes it is in the best interest of the subject to be removed from the trial.

Patients may be withdrawn from the trial if a serious adverse event occurs. The date and reason for discontinuation should be noted on the CRF. Subjects who discontinue prematurely should be seen for a final evaluation and the Sponsor should be notified immediately.

## 5.6 Premature Termination of Trial/Closure of Center

The IND sponsor may discontinue the trial at any time. Reasons for discontinuation may include, but are not limited to, new information on safety or efficacy, requests from regulatory authorities, or changes in business priorities. Additional reasons for center closure may include, but are not limited to, excessive protocol violations, inadequate regard for subject safety, failure to follow recommended procedures (e.g., documentation), failure to accommodate Avid/CRO monitors or to provide required access to data and source documents, staff turnover or inadequate staffing, and inadequate enrollment. Except in cases affecting subject safety, the investigators will be given a minimum of 30 days to complete final study evaluations for ongoing subjects. In all cases of center or study termination, appropriate steps will be taken to ensure subject safety.

# 6. WARNINGS/PRECAUTIONS

The most up-to-date and complete information regarding the use of florbetapir F 18 can be found in the investigator's brochure.

In brief, florbetapir F 18 is an imaging agent that will be used at relatively low (tracer) doses. Subjects receiving florbetapir F 18 will be followed closely by means of adverse event reporting and vital signs. In the event of a study related adverse event, subjects should not be discharged until the event has resolved or stabilized.

The most common side effect in completed studies was headache. Additional uncommon side effects reported were nausea, dysgeusia (bad taste in the mouth), flushing, pruritus (itching), urticaria (hives), and infusion site rash. Musculoskeletal (muscle and bone) pain in the neck, shoulder, and back, fatigue, anxiety, claustrophobia (fear of being in closed or narrow spaces), insomnia (inability to sleep), dizziness, chills/feeling cold, and hypertension (high blood pressure) were also reported. Because these events could be related in part to the PET scan apparatus and procedures, careful attention should be taken to make the subject aware of the planned procedures and to maximize subject comfort in the scanner. Previous human clinical trials have revealed no clinically meaningful changes in vital signs, ECG or laboratory changes.

# 7. PROCEDURES AND METHODS

## 7.1. Assessment Periods (See Flow Chart, Appendix 11.2)

***Screening Day:***

Screening may take place over several days. All screening assessments will preferably be performed within 30 days prior to the PET imaging session. Some screening assessments may be performed on imaging day prior to injection with sponsor approval. Screening assessments will include:

- Informed consent;
- Demographics (age, gender, education, race, ethnicity);
- Medical history, concomitant medications;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of relevant neurologic disease);
- Cognitive status interview, including MMSE;
- Where appropriate, informant interview with family member or close friend who is familiar with subject's everyday functioning abilities;
- Urine pregnancy test (women of childbearing potential); and
- A physician will see the patient during the screening visit.

Demographic information, cognitive status assessment or MMSE collected within the last 30 days as part of a companion protocol or clinic visit need not be repeated.

***Imaging Day:***

The following assessments will be performed for all subjects:

- Females of childbearing potential will have a urine pregnancy dipstick test prior to injection (the result must be negative for the subject to be administered florbetapir F 18);
- Vital signs will be taken in a supine position immediately prior to administration of florbetapir F 18 (within 30 minutes prior to injection). Body weight will be measured with the subject lightly clothed;
- A 370 MBq bolus injection of florbetapir F 18 will be administered and 10 minute continuous brain PET imaging will begin 50 minutes post-injection. The images will be reconstructed immediately after the 10 minute scan, and if any motion is detected, another 10 minute continuous scan will be acquired. Sites with dynamic PET acquisition capabilities may elect to acquire a 20 minute acquisition, beginning 30 to 50 minutes post injection. If a 20 minute acquisition is chosen, the site will reconstruct at least one 10 minute image from the dataset in addition to a 20 minute reconstruction. All datasets will be submitted to the sponsor for analysis. Sites may elect additional imaging timepoint with prior sponsor approval;
- With prior sponsor approval and at the discretion of the investigator, a subgroup of not more than 5 subjects will be given the option of having a regimen of arterial blood sampling with up to 70 minutes of imaging beginning immediately after florbetapir F 18 administration. See Appendix 11.4 for detailed instructions on arterial blood sampling;
- Subjects will be observed continuously for signs of adverse events or serious adverse events;
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected; and
- A physician or physician designee will see the patient prior to dosing and prior to discharge.

***Follow-Up:***

Each study participant will be contacted by phone 24–72 hours after they were injected with the investigational agent to confirm their well-being and query them about any new adverse events that may have occurred within 24 hours post-injection.

***Repeat Imaging:***

Longitudinal imaging studies may be conducted under protocol $^{18}$F-AV-45-A14, with prior sponsor approval and at the discretion of the investigator. In these studies subjects may have up to two imaging sessions within a 12 month timeframe. Procedures for each day will be identical to those described above.

## 7.2. Observations and Measurements

Informed Consent

Potential volunteers, authorized representatives, caregivers and guardians (if applicable) will be allowed to read a written informed consent form. The principal investigator or designee will explain all study procedures and risks to the volunteer. The volunteer will have an opportunity to have all questions answered. The appropriate parties will then sign and date the informed consent form, indicating willingness to participate in the study (see Section 7.5). A copy of the signed informed consent will be given to the volunteer or caregiver.

All informed consent forms must be approved by Avid and the appropriate IRB prior to use.

Medical History, AD History

At the screening visit, the investigator or designee will obtain a case history which will include the following information:

- Relevant demographic information;
- Relevant medical and surgical history;
- Concurrent medications;
- Disease history (month and year of symptom onset, month and year of diagnosis); and
- Family history of relevant neurologic disease (history of dementia, stroke, Parkinson's, Huntington's or related neurologic disease in siblings and parents).

Vital Signs

Vital signs (blood pressure, pulse, respiratory rate) will be taken on the day of the scan, immediately prior to administration of florbetapir F 18 (within 30 minutes before injection). Blood pressure, pulse and respiratory rate should be taken in the supine position. At the imaging visit body weight will be measured with the subject lightly clothed.

MMSE (Folstein et al., 1975)

The MMSE will be performed at the screening visit.

If the MMSE was collected within the last 30 days as part of a companion protocol or clinical visit it need not be repeated.

Physician Visit

A physician must see the subject during the screening day visit. A physician or physician designee must see the subject on imaging day prior to drug administration and prior to discharge. At this time, the physician or designee should review all safety data and briefly examine/query the subject regarding potential adverse events or other treatment issues.

## 7.3. Protocol for Image Collection & Analysis

The investigators and the sponsor will prepare and distribute an Image Management Plan for image acquisition procedures and parameters prior to the start of the study.

Images will be evaluated qualitatively and/or quantitatively:

- Images will be visually examined by a trained radiologist or nuclear medicine physician who is blinded to the subject diagnosis and will be reported as either Aβ positive or Aβ negative.

- SUV for target areas such as frontal cortex, temporal cortex, parietal cortex, posterior cingulate cortex, anterior cingulate and precuneus, and reference regions including cerebellum will be calculated. SUVR for cortical target areas relative to cerebellum will also be calculated.

## 7.4. Good Clinical Practice and Monitoring

All clinical studies performed under the direction of Avid will be conducted in accordance with the Code of Federal Regulations (CFR) and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and Avid/CRO Standard Operating Procedures (SOP). This includes:

1. IRB approval: An investigation will be initiated at a study site only after the IRB for that study site has given their written approval of the protocol and informed consent;

2. Informed Consent: Study procedures will not be initiated until the subject and/or their caregiver (as appropriate) signs the IRB approved informed consent form;

3. Recording and monitoring of adverse events as outlined in Section 7.7.1 & 7.7.3 including the notification of study site clinical investigators, IRBs and

the FDA regarding serious adverse event;

4. Avid's obligation to monitor the participating center on a regular basis; and

5. The termination of a center or the trial if conditions apply, as outlined in Section 5.6.

## 7.5. Informed Consent and Subject Information

Potential subjects, their legally authorized representative and caregiver/informant will be allowed to read a written informed consent form. The principal investigator or designee will explain all study procedures and risks. The subject and caregiver will have an opportunity to have all questions answered by a study physician. The subject and/or the authorized representative will then sign and date the informed consent form, indicating willingness to participate in the study.

Patients with AD are potentially a vulnerable population with compromised mental capacity. Investigators should take extra care to evaluate a patient's ability to give consent. If the subject is capable of giving informed consent then the subject should sign on the consent line of the informed consent form.

If the subject is not capable of giving consent, consent may be given by an authorized representative. However, it is expected that all subjects entering this study should at least have the capacity to understand that they are engaging in a research study and should affirm that they do not object to participating, by signing on the subject assent line of the consent form.

All informed consent forms must be approved by Avid or designee, and by the appropriate IRB. No study related procedures shall be performed prior to completion of the informed consent process, and signing of the informed consent form. A copy of the signed informed consent should be given to the patient and/or their caregiver for their records.

## 7.6. Documentation

PET scan results will be saved in appropriate electronic format. A copy of the image data will be saved at the site and a copy will be forwarded to the sponsor or to the designated imaging core laboratory.

All other data required by the protocol will be recorded in the CRF. All data in the CRF will be substantiated by "source documents," which consist of the subject's medical files, laboratory result sheets, etc. All source documentation must be available to Avid and designees. Completed source documents and CRFs may need to be made available for an audit by the FDA or other international regulatory authorities or Avid or designee at any time. CRFs and all other records must be filed in accordance with applicable laws and regulations (see Section 10.6).

## 7.7. Adverse Events (AE)

Avid's standards for recording and reporting adverse events (AEs) are to be followed regardless of applicable regulatory requirements that may be less stringent. All AEs must be fully recorded on the Adverse Event Page of the CRF. Investigators will be instructed to report to Avid or its designee their assessment of the potential relatedness of each AE to investigational product or drug delivery system via electronic data entry. If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Avid or its designee via electronic data entry the circumstances and data leading to any such dosage reduction or discontinuation of treatment. In cases where the investigator notices an unanticipated benefit to the patient, study site personnel should report "unexpected benefit" with the actual event term to Avid or its designee (for example, the complete actual term would be "unexpected benefit—sleeping longer").

Laboratory test abnormalities considered by the Investigator to be clinically relevant should be reported on the Adverse Event page of the CRF. Signs and symptoms of each AE should be described in detail (e.g., start and stop dates, severity, intensity, relationship to investigational product, action taken, and outcome). Additionally, any clinically significant findings from laboratory evaluations, vital sign measurements, or other study procedures that result in a diagnosis should be reported as an AE to Avid or its designee.

Cases of pregnancy that occur during maternal or paternal exposures to investigational product or drug delivery system should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

### 7.7.1. *Adverse Event Monitoring*

Each subject must be carefully monitored for adverse events. An assessment must be made of the seriousness, intensity, and relationship to the administration of the trial medication.

### 7.7.2. *Adverse Event Definitions*

Adverse Events (AE)

An AE is any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational product.

For reporting purposes, Avid will distinguish among pre-existing conditions, trial-emergent AEs, and treatment-emergent AEs. The end of study for the purpose of adverse event reporting is defined as 24 hours after administration of florbetapir F 18 injection.

Pre-existing conditions (i.e., undesirable experiences, signs, or symptoms that begin prior to the Screening Visit) will be recorded on the medical history and/or physical exam pages. These conditions will not be entered on the AE pages unless they worsen in intensity or frequency after the Screening Visit and before the Imaging Visit.

Trial-emergent AEs are undesirable experiences, signs or symptoms that begin, or worsen in intensity or frequency, on or after the Screening Visit, and prior to administration of study drug at the imaging visit. These will be recorded on the AE pages.

Treatment-emergent AEs are undesirable experiences, signs, or symptoms that begin or worsen in intensity or frequency at the time of or after the administration of study drug, defined in this protocol as 24 hours after florbetapir F 18 injection. These will be recorded on the AE pages.

Serious Adverse Event (SAE)
An SAE is any AE from this study that results in one of the following outcomes or constitutes one of the following events:

- Death;
- Initial or prolonged inpatient hospitalization (other than that required by protocol; "social hospitalization" or any hospitalization for non-medical reasons does not constitute an SAE);
- A life-threatening experience (that is, immediate risk of dying);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect;
- Occurrence of seizure or seizure-like event;
- Considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse event (SAE) collection begins after the patient has signed informed consent and has received the investigational product. An SAE spontaneously reported to have occurred within 24 hours of florbetapir F 18 administration will be reported, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either investigational product or drug delivery system, or a protocol procedure

Unexpected Adverse Event

An unexpected AE is an AE not previously reported or an AE that occurs with specificity, severity or frequency that is not consistent with the current investigator's brochure.

Relationship to Investigational Product

The assessment of the relationship of an AE to the administration of the study drug (remote, possible, and probable) is a clinical decision based on all available information at the time of the completion of the CRF. The following definitions of the relationship between the study drug and the AE (including SAEs) should be considered:

- *Remote (unlikely, doubtful, improbable):*
  Another cause (concomitant drugs, therapies, complications etc.) is probable.

- *Possible:*
  The time course between the administration of the study medication and the occurrence or worsening of the AE is consistent with a causal relationship but another cause (concomitant drugs, therapies, complications etc.) cannot be ruled out;

  or

  The time course between the administration of the study medication and the occurrence or worsening of the AE is not consistent with a causal relationship but no alternative cause can be identified.

- *Probable:*

  The time course between the administration of the study medication and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause can be identified (concomitant drugs, therapies, complications etc.).

If the Investigator is unable to assess causality, the AE should be considered "Possible" by definition and not "Remote".

Intensity/Severity of an Adverse Event

In addition to assessing the relationship of the administration of the investigational product to AEs, an assessment is required of the intensity (severity) of the event.

The following classifications should be used:

- *Mild:*
  A mild AE is an AE, usually transient in nature and generally not interfering with normal activities.

- *Moderate*:
  A moderate AE is an AE that is sufficiently discomforting to interfere with normal activities.

- *Severe:*
  A severe AE is an AE that incapacitates the subject and prevents normal activities. Note that a severe event is not necessarily a serious event. Nor must a serious event necessarily be severe.

### 7.7.3. *Adverse Event Documentation*

All AEs must be fully recorded on the Adverse Event Page of the Case Report Forms. Documentation must be supported by an entry in the subject file. Signs and symptoms of each AE should be described in detail (e.g., start and stop dates, severity, intensity, relationship to investigational product, action taken, and outcome).

Adverse events fulfilling the definition of an SAE should also be recorded on the Serious Adverse Event Reporting Form.

### 7.7.4. *Reporting of Serious Adverse Events*

Study site personnel must alert Eli Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms.

Serious adverse events occurring after a subject has taken the last dose of investigational product will be collected 24 hours after the last dose of investigational product, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either investigational product or drug delivery system, or a protocol procedure.

If a patient experiences an SAE after signing informed consent, but prior to receiving investigational product, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure. Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

# 8. STATISTICAL ANALYSIS

## 8.1. General Statistical Considerations

All values will be summarized by diagnostic group: cognitively normal volunteers, patients with AD, patients with MCI and where relevant, other disorders as determined by the companion protocol. Guidelines for diagnostic classification of cognitively normal volunteers, subjects with MCI and subjects with AD can be found in Appendix 11.3.

Frequency distributions including counts and percents will be included for all categorical outcomes. Summary statistics including mean, standard deviation, median, minimum and maximum values will be presented for all continuous outcomes.

Additional details concerning statistical analyses will be included in the Statistical Analysis Plan (SAP) to be completed prior to the end of enrollment into the study.

## 8.2. Populations for Analysis

The efficacy population will include all patients for whom image data are available. All analyses involving amyloid imaging outcomes will be based on the efficacy population.

## 8.3. Endpoint Definitions

**Efficacy (Imaging Results)**

- Qualitative assessment of image (Aβ+ or Aβ-)
- Quantitative assessment (SUVR) associated with the following brain regions:
  - Frontal cortex
  - Temporal cortex
  - Parietal cortex
  - Posterior cingular cortex
  - Anterior cingulate
  - Precuneus
  - Global average of all of the above

## 8.4. Analyses

### 8.4.1 Demographic, Baseline Characteristics and Cognitive Scales

Frequency distributions and summary statistics for demographic and baseline variables will be presented by diagnostic group and for all subjects combined. Key demographic and baseline characteristics to be summarized

include, but are not limited to: age, gender, education, race, and disease history.

Summary statistics for MMSE will be presented by diagnostic group and overall.

### 8.4.2 Safety Analyses

Adverse events including injection site reactions will be summarized in terms of number and percentage of patients experiencing an AE. The summary will be further broken down by system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) terms. Adverse events will also be presented by severity, relationship to treatment, and seriousness. All patients who experience SAEs or who discontinue due to AEs will be summarized.

### 8.4.3 Qualitative assessment of images

Frequency distributions and summary statistics for qualitative (% Aβ+ or Aβ-) will be presented by diagnostic group. The frequencies will also be compared between diagnostic groups using Chi-Square testing. Fisher's exact test will be used if any table cell has a frequency count less than or equal to 5.

### 8.4.4 Quantitative assessment of images

SUVR measurements will be summarized by diagnostic group and by brain region. Unless otherwise specified, all analyses will be performed on each brain region separately.

Analysis of variance (ANOVA) will be used to compare the mean SUVR values between diagnostic groups. If the prerequisites of ANOVA is violated (such as homoscedasticity of variance), then Kruskal Wallis test will be used.

## 9. USE OF DATA AND PUBLICATION

Avid adheres to the Pharmaceutical Research and Manufacturers of America (PhRMA) Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results. A complete copy of these principles is available from Avid and can also be found at the PhRMA website (http://www.phrma.org). Our policy is briefly summarized below:

- We commit to timely communication of meaningful results of controlled clinical trials, regardless of outcome.
- As a sponsor, we may recommend that the Investigator(s) delay or decline publication in cases where the study design, conduct, or data are insufficient to

allow meaningful interpretation. Avid and the Investigator(s) will discuss the study design and data in advance of the study, and again after completion, and will strive, through appropriate scientific debate, to reach a consensus regarding the potential merits of publication.

- Avid retains the right to review any manuscripts, presentations, or abstracts before they are submitted for publication. Where differences of opinion or interpretation exist regarding data planned for publication, the parties (Avid and the Investigator) should try to resolve them through appropriate scientific debate. Avid retains the right to delay publication for up to 60 days to protect intellectual property.
- Anyone who provides substantial contributions should receive appropriate recognition as an author or contributor when the manuscript is published.

## 10. INVESTIGATOR'S REGULATORY OBLIGATIONS

All clinical work conducted under this protocol is subject to GCP rules; this may include an inspection by Avid and/or Health Authority representatives (FDA or international regulatory authorities) at any time.

### 10.1. Institutional Review Board (IRB)

The intent of the research program, the trial protocol, the subject information/informed consent form and any advertising material used to recruit subjects must be submitted to the clinical investigator's IRB, and its approval must be obtained prior to the start of the trial. A copy of the approval must be forwarded to Avid. When necessary, an extension or renewal of IRB approval must be obtained and also forwarded to Avid.

### 10.2. Informed Consent

A signed, written informed consent must be obtained from each subject as described above. A copy of the local IRB's approved version of the informed consent form must be forwarded to Avid or designee for review prior to being used to obtain subject consent.

### 10.3. Protocol Adherence

The protocol must be read thoroughly and the instructions must be followed exactly. Where a deviation occurs for the well-being of the subject, it must be documented, the sponsor/monitor informed, and a course of action agreed upon.

## 10.4. Documents Necessary for Initiation of the Trial

Avid must be provided with the following documents prior to the enrollment of any subjects:

- Original signed and dated Investigator's Agreement to Protocol page;
- Original signed and dated statement of responsibility for the conduct of the study by the Principal Investigator (FDA Form1572);
- Curriculum vitae (signed and dated within the past 2 years) and financial disclosure form for the principal investigator and all staff listed in Box #6 on the FDA Form 1572;
- Copy of the IRB and radiation safety committee approval (if applicable);
- Copy of the IRB stamped approved consent form;

## 10.5. Investigational Product Control

The receipt of clinical supplies (i.e. starting material for florbetapir F 18) must be documented at the site.

All drug supplies for this trial should be retained in a safe and secure place at all times during the trial. Florbetapir F 18 Injection should be prepared by a qualified radiopharmacist/chemist under Good Manufacturing Practices (GMP) conditions and dispensed by the pharmacist, the investigator, or by a qualified individual under the investigator's supervision. An up-to-date drug inventory/dispensing record must be maintained. All drug supplies must be accounted for. At the end of the trial, the monitor will retrieve a copy of the drug inventory/dispensing record and will return it to Avid. The original must be retained in the study file.

After completion of the trial, all remaining clinical supplies must be returned to the sponsor or their representative.

## 10.6. Data Collection

Case report forms (CRF) will be used for this trial. Individual subject files should include appropriate source documents, including but not limited to subject's medical records, and laboratory test results. The files should include information such as visit dates, records of medical history, examinations administered, concomitant treatment, any adverse event encountered and other notes as appropriate. These constitute "source data". All entries on the CRFs must be backed up by source data. Original electronic versions of imaging studies are also considered source data and should be kept on file by the site, and appropriate copies should be forwarded to the sponsor/CRO for analysis as specified in the Image Management Plan.

Each subject's source file should include an original signed informed consent form. When the trial is completed, the informed consent form should be kept on file with

other trial related records.

The CRFs must be kept in order and up-to-date so that they always reflect the latest observations on the subjects that are enrolled in the trial. CRFs must be completed legibly for each subject enrolled in the trial and signed by the investigator. This should be done as soon as possible after completion of the patient's participation in the trial. A monitor will review the CRFs and source verify all information on the CRF.

## 10.7. Adverse Events

All AEs encountered during the clinical trial must be documented on the CRF, whether or not considered drug-related.

Eli Lilly must be notified immediately (as soon as possible, and in all cases within 24 hours) of a drug experience, condition, development, or event, which is considered serious. Eli Lilly must be notified immediately of any findings with the use of the drug that may suggest significant hazards, contraindications, adverse drug reactions (ADRs) and precautions pertinent to the safety of the drug. The investigator will be requested to complete a separate report form in addition to the information on the eCRF. See section 7.7.4 for reporting SAEs.

If an SAE is determined to be unexpected (not previously reported or described by Avid), and study drug-related, Eli Lilly, will notify the investigator in writing. The investigator should forward this notification to the IRB within 24 hours of receipt.

## 10.8. Records Retention

All correspondence (e.g., with Avid, IRB, etc.) relating to this clinical trial should be kept in appropriate file folders. Records of subjects, source documents, CRFs, and drug inventory sheets pertaining to the trial must be kept on file. Records must be retained for 2 years following the date of the last marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, records should be kept for 2 years after the IND is considered by the FDA to be officially withdrawn.

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person who will accept the responsibility. Notice of transfer must be made to and agreed upon by Avid, prior to transfer.

# 11. APPENDICES

## 11.1. References

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## 11.2 Trial Flow Chart

| Evaluations | Screen | Pre-dose | Dose | Injection Circulation (0 – 50 minutes)[3] | Continuous PET Imaging 10 minutes | End of Imaging | 24-72 hours post injection |
|---|---|---|---|---|---|---|---|
| **Signed Consent** | X | | | | | | |
| **Medical / Disease History** | X | | | | | | |
| **Concomitant Meds** | X | X | | | | | |
| **MMSE** | X | | | | | | |
| **Physician Visit** | X | X[1] | | | | X[1] | |
| **Vital Signs** | | X | | | | | |
| **Urine Pregnancy Test** | X | X | | | | | |
| **Florbetapir F 18 Administration** | | | X | | | | |
| **PET Imaging[2]** | | | | | **Continuous 10 minute scan - 50 minutes after dose injection** | | |
| **Follow-up Phone Call** | | | | | | | X |
| **Adverse Event Assessment** | X | X | X | X | X | X | X[3] |

[1]A physician designee may see the subject prior to injection and at discharge on imaging day.
At the imaging visit body weight will be measured with the subject lightly clothed.
[2] Sites with dynamic PET acquisition capabilities may elect to acquire a 20 minute acquisition, beginning 30 to 50 minutes post injection. Sites may elect additional imaging timepoints with prior sponsor approval
[3] Collect information about any new adverse events that may have occurred within 24 hours post-injection

## 11.3 Guidelines for diagnostic classification

Patients meeting the NINCDS-ADRDA criteria (McKhann et al., 1984) should be classified as probable AD. In particular:

1. Patients with mild/moderate dementia as evidenced by a MMSE score ranging from 10 to 24, boundaries included, at screening;
2. Patients whose history of cognitive decline has been gradual in onset and progressive over a period of at least 6 months. Evidence should be present indicating sustained memory deterioration in an otherwise cognitively normal patient, plus additional impairment in another cognitive function such as: orientation, judgment and problem solving, or functioning in personal care;

Subjects who meet the following criteria should be classified as mild cognitive impairment:

1. Patients with complaint of memory or cognitive decline corroborated by an informant;
2. Patients with a CDR of 0.5;
3. Patients with objective cognitive impairment or marginally normal cognition with a documented history of high cognitive performance;
4. Have no obvious caused for their cognitive impairment (e.g., onset coincides with recent head trauma or stroke);
5. Have sufficiently preserved general cognition and functional performance such that a diagnosis of AD cannot be made at the time of the screening visit;
6. Patients with essentially normal ADL;
7. Patients who are not demented;
8. Patients with an MMSE score > 24;

Subjects who meet the following criteria should be classified as cognitively normal volunteers:

1. Subjects with an MMSE score $\geq$ 29, and are cognitively normal based on history (no evidence of significant recent cognitive decline) and psychometric test battery at screening;

**Note:** Subjects with dementia who do not meet criteria for probable AD, as described in point number 1, should be classified as 'other dementing disorders'.

## 11.4 Arterial Sampling

A maximum of 5 study subjects may have an optional arterial catheter placed for plasma sampling and construction of an arterial $^{18}$F-AV-45 input function. If a study participant agrees to having the optional arterial catheter placed, the study physician will examine the patient at screening and at baseline and will make a determination whether the patient is a candidate for arterial sampling. Subjects that have a history of bleeding disorders, are taking anticoagulant drugs, have a history of peripheral vascular disease or clotting disorder and subjects who have other medical or behavioral conditions that, in the opinion of the investigator, would result in elevated risk of complication during the sampling process will not be considered as candidates for the arterial sampling subgroup. Additionally, in order to be eligible for arterial sampling, patients with Alzheimer's disease must have a caregiver who is continuously available for at least 6 hours following the end of the study to report on possible procedure related complications. Subjects do not have to qualify for arterial sampling in order to participate in the study. If a subject qualifies for arterial sampling, but a radial artery cannula cannot be placed, the subject may still participate in the imaging protocol. Similarly, subjects who experience discomfort or have difficulty tolerating the arterial sampling procedure may discontinue this part of the study, but may continue the imaging protocol.

Procedure:

- A 25 ga plastic catheter will be placed percutaneously in the radial artery. Arterial cannulation will be performed by an individual trained and experienced in the technique. Local anesthesia and sterile technique will be utilized to minimize discomfort and the risk of infection. If the radial artery cannot be cannulated, the subject will be excluded from the arterial sampling subgroup.

- A physician will be immediately available throughout the imaging session for evaluation of potential complications. Any significant complications arising from the radial cannulation will be noted and reported to the IRB, sponsor and FDA as appropriate.

- The catheter will be removed by a trained individual at the end of the imaging session and local pressure applied for approximately 5 min. A pressure bandage will then be applied and instructions given to the patient and caregiver to leave in place for 24 hr. The adequacy of local hemostasis and absence of ischemic changes in the hand will be verified by the PET technologists and a physician will see the patient prior to discharge.

- Prior to discharge, subjects and their caregivers will be instructed regarding potential complications (i.e., bleeding, clot formation and infection). Subjects and their caregivers will be reminded of the phone number for the investigator (in the consent form) and the study coordinator, and given instruction to phone the

investigator should any adverse experience occur and return to the hospital should treatment be required.

- In the unlikely event of an ischemic complication, medical treatment with the use of either thrombolytic drugs and/or vascular surgery would be initiated.

- Infectious complications will be managed with the parenteral administration of antibiotics.

## INVESTIGATOR'S AGREEMENT TO PROTOCOL

**Protocol:** $^{18}$F-AV-45-A14: Clinical Evaluation of Florbetapir F 18 ($^{18}$F-AV-45)

**Date and Version: February 1, 2013 – Amendment #3**

**I agree to conduct the study according to this protocol and to comply with its obligations, subject to ethical and safety considerations and all applicable regulations (ICH, CFR).**

**I shall not disclose the confidential information contained in this protocol or any results obtained from the study, except for publication in accordance with Section 9 of this protocol, without written authorization from Avid.**

**Principal Investigator:**

_____ _____

Printed Name Date

_____

Signature