

18F-AV-1451-A05 Protocol Amendment 2

An Open Label, Multicenter Study, Evaluating the Safety and Imaging Characteristics of 18F-AV-1451 in Cognitively Healthy Volunteers, Subjects With Mild Cognitive Impairment, and Subjects With Alzheimer's Disease

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Date and Version:

07 August 2015, Amendment 2

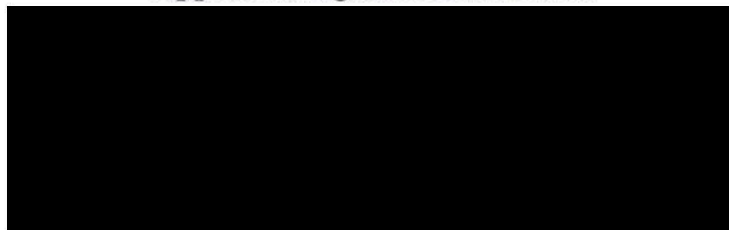
Name of Compound:

¹⁸F-AV-1451 ([F-18]T807)

Sponsor:

Avid Radiopharmaceuticals, Inc.
Philadelphia, Pennsylvania USA

Approvals/Signatures and Date:



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Sponsor: Avid Radiopharmaceuticals, Inc.	Name of Compound: ¹⁸ F-AV-1451([F-18]T807)	Active Ingredient(s): 7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole
Title of Study: ¹⁸ F-AV-1451-A05 An open label, multicenter study, evaluating the safety and imaging characteristics of ¹⁸ F-AV-1451 in cognitively healthy volunteers, subjects with Mild Cognitive Impairment, and subjects with Alzheimer's disease		
Planned number of subjects (Enrolled): 380 The first Phase of the study will be divided into three groups: <ol style="list-style-type: none"> 1. Cognitively healthy volunteer subjects <ol style="list-style-type: none"> a. Approximately 20 subjects ≥ 20 to ≤40 years of age b. Approximately 60 subjects ≥ 50 years of age 2. Mild cognitive impairment (MCI) (n=80) 3. Alzheimer's disease (AD) subjects <ol style="list-style-type: none"> a. Approximately 60 subjects with an MMSE ≥ 20 b. Approximately 10 subjects with an MMSE >10 and <20 The second Phase of the study will enroll: <ol style="list-style-type: none"> 4. Approximately 150 subjects with cognitive impairment (MCI or demented subjects with a suspected neurodegenerative cause) and an MMSE ≥ 20 and ≤ 27. For the purposes of ensuring a distribution of disease severity, a target of at least 1/3 of the enrolled subjects will have dementia. 		
Name of compound: ¹⁸ F-AV-1451(also known as [F-18]T807) Dose: 370 MBq (10 mCi) Route of Administration: Intravenous (IV) bolus		
Study Phase: II		
Study Centers: Approximately 30 centers in the United States		
Trial Objectives: This study will be conducted in two phases, an exploratory phase and a confirmatory/validation phase, which will have separate subjects and analyses. The first phase of this study will be comprised of a cross-sectional component and a longitudinal component.		

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<p>The second (confirmatory/validation) phase will focus on the relationship of baseline PET tau images to changes in longitudinal clinical measures.</p> <p>Exploratory Phase, Cross-sectional objectives:</p> <p>The primary objective of the cross-sectional component is:</p> <ul style="list-style-type: none"> To compare ¹⁸F-AV-1451 imaging results in subjects with AD to subjects with MCI and cognitively healthy older individuals <p>The secondary objective of the cross-sectional component is:</p> <ul style="list-style-type: none"> To establish a database of cognitively healthy individuals to show the spectrum of ¹⁸F-AV-1451 imaging results in cognitively healthy individuals across a range of age strata <p>Exploratory objectives of the cross-sectional component are:</p> <ul style="list-style-type: none"> To determine whether greater degrees of cognitive impairment correlate with higher ¹⁸F-AV-1451 uptake in subjects with an amyloid positive status To explore whether tests of specific cognitive domains correlate with regional ¹⁸F-AV-1451 uptake To explore the relationships between ¹⁸F-AV-1451 uptake and biomarkers of neurodegeneration and neurological disease (CSF markers including tau, phospho-tau and beta-amyloid (Aβ), genetic markers, PET amyloid imaging, and brain atrophy assessed by volumetric MRI) To expand the ¹⁸F-AV-1451 safety database <p>Exploratory Phase, Longitudinal objectives:</p> <p>The primary objective of the first phase longitudinal component is:</p> <ul style="list-style-type: none"> To assess the rate of change of tau deposition as measured by ¹⁸F-AV-1451 uptake over time. <p>Exploratory objectives of the first phase longitudinal component are:</p> <ul style="list-style-type: none"> To explore associations between changes in ¹⁸F-AV-1451 uptake in the brain and clinical and functional measures, as well as, biomarkers of neurodegeneration and neurological disease (CSF markers including tau, phospho-tau and beta-amyloid (Aβ), genetic markers, PET amyloid imaging, and brain atrophy assessed by volumetric MRI). To expand the ¹⁸F-AV-1451 safety database <p>Confirmatory Phase, Longitudinal objectives:</p>		

Sponsor: Avid Radiopharmaceuticals, Inc.	Name of Compound: ¹⁸ F-AV-1451([F-18]T807)	Active Ingredient(s): 7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole
<p>The second phase of the study is designed to provide independent validation of the relationships observed in the exploratory analyses of the first phase. In particular, the goal of the second phase is to confirm the relationship between ¹⁸F-AV-1451 uptake in the brain as measured by PET and the subsequent rate of cognitive decline observed over longitudinal follow up.</p>		
Eligibility: Each of the groups is comprised of specific inclusion and exclusion criteria to determine patient eligibility. See Section 5.3, Selection of Subjects.		
Study Design: <p>This is a phase 2 cross-sectional and longitudinal observational study that will evaluate imaging characteristics of ¹⁸F-AV-1451 in control subjects and patients with MCI and AD. This study will be conducted in two phases, an exploratory/hypothesis generating phase and a confirmatory/validation phase, which will have separate subjects and analyses.</p> <p>All subjects will provide informed consent before starting any study procedures.</p> <p>For both the Exploratory and Confirmatory Phases, screening assessments may take place over several days and will include demographic information, cognitive testing, safety assessment, and MRI, including both volumetric and standard clinical sequences. Raters administering the cognitive testing will be blinded to the ¹⁸F-AV-1451 scans for subjects in the Confirmatory Cohort. Subjects who qualify for the study will return to the clinic at a later date for a florbetapir F 18 PET imaging session and an ¹⁸F-AV-1451 PET imaging session. Some subjects, who are ≥ 50 years of age, in the exploratory phase may have the option to also participate in cerebrospinal fluid (CSF) collection by lumbar puncture (LP).</p> <p>Subjects who are ≥ 50 years of age will return for follow-up visits at 9 (+/-2) and 18 (+/-2) months following the initial ¹⁸F-AV-1451 scan. Cognitive assessments and updates to concomitant medications and medical history will be collected at each follow-up visit. Subjects in the Exploratory phase will also have follow-up ¹⁸F-AV-1451 scans and MRI, including both volumetric and standard clinical sequences. A sub-set of subjects in the Exploratory phase may have the option to have an additional resting state functional (rsf)MRI sequence scan in addition to the volumetric and standard clinical sequences at both the screening MRI and follow-up MRIs. Subjects or their designated decision maker will be contacted by phone at 5 and 14 months following the initial ¹⁸F-AV-1451 scan to collect updated concomitant medications and medical history.</p>		

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<p>Assessments and Endpoints:</p> <p>Each group will have a screening visit(s), a florbetapir F 18 PET imaging visit, a ¹⁸F-AV-1451 PET imaging visit, and follow-up phone calls after each imaging visit.</p> <p><i>Florbetapir F 18 PET Imaging Session:</i></p> <p>For the florbetapir F 18 PET imaging session, subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of florbetapir F 18. At 50 minutes following injection, a continuous 10-minute brain scan (2 acquisitions of 5 minute duration) will begin.</p> <p><i>¹⁸F-AV-1451 PET Imaging Session:</i></p> <p>For the ¹⁸F-AV-1451 PET imaging session, subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of ¹⁸F-AV-1451 At approximately 80 minutes post dose, scanning will begin. Four 5-minute acquisitions will be taken.</p> <p>For both imaging sessions adverse events will be monitored continuously during the imaging session. Subjects who experience any adverse event during an imaging session will not be discharged until the event has resolved or stabilized.</p> <p>A follow-up phone call to the subject, or designated decision maker, will be conducted within 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.</p> <p>In the Exploratory longitudinal component, subjects who are ≥ 50 years of age will have two longitudinal follow-up visits with ¹⁸F-AV-1451 PET imaging, MRI, cognitive assessments and updated medical history and concomitant medications. In the Confirmatory Cohort, longitudinal follow-up visits will consist of cognitive assessments and updated medical history and concomitant medications. No PET imaging or MRI is planned at the follow-up visits in the Confirmatory Cohort. Additional assessments that will be performed at each visit are detailed in Section 7.1.</p>		

Statistical Methods:

In the exploratory study phase, descriptive statistics will be applied to describe the ¹⁸F-AV-1451 SUVR distribution across age groups among cognitive healthy subjects. ANOVA analysis will be applied to detect the difference between clinical diagnosis groups. Analyses will be conducted to assess the relationship among ¹⁸F-AV-1451 uptake, cognitive function measurements, and other collected biomarkers. Longitudinal data from the exploratory study phase will be assessed periodically to determine the relationships between various ¹⁸F-AV-1451 imaging parameters (e.g., composite and regional SUVR, voxel based statistics and visual interpretation) and the change from baseline in the various cognitive and functional assessments. These data will be used to generate hypotheses regarding the relationship between ¹⁸F-AV-1451 PET tau imaging and cognitive/functional change that will be formally incorporated into an analysis plan and tested in the confirmatory phase of the study.

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ABBREVIATIONS AND DEFINITIONS

Aβ	Beta amyloid
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale- Cognitive Subscale
Adverse Event (AE)	Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
CHO	Chinese Hamster Ovary
Case Report Form (CRF) and electronic Case Report Form (eCRF)	A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CNS	Central Nervous System
CRO	Contract Research Organization: A person or organization (commercial, academic, or other) contracted by the sponsor to perform one or more of the sponsor's trial-related duties and functions.
CT	Computed Tomography
DSST	Digit Symbol Substitution Test
Efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.
FDA	US Food and Drug Administration
FDG	¹⁸ F - Fluorodeoxyglucose

GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
Institutional Review Board /Independent Ethics Committee	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare and human rights of the subjects participating in a clinical study are protected.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	Intravenous
K_d	Dissociation Constant
MAO	Monoamine Oxidase
MBq	Megabecquerel
mCi	Millicurie
MCI	Mild Cognitive Impairment
MHD	Maximum Human Dose
MRI	Magnetic Resonance Imaging
NOAEL	No Observable Adverse Effect Level
NOEL	No Observable Effect Level
PET	Positron Emission Tomography
SUVR	Standard Uptake Value Ratio

1. INTRODUCTION

Molecular imaging biomarkers have the potential to aid in the diagnosis of patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) (Dubois, 2010; McKhann, 2011). Positron emission tomography (PET) ligands such as florbetapir F 18 (Wong, 2010) may provide a minimally invasive estimate of cortical beta amyloid (A β) neuritic plaque deposition, a hallmark pathology, and a required element for the evaluation of AD neuropathologic diagnosis (Hyman 2012). Multiple studies comparing amyloid PET scans to histopathologic assessment of amyloid burden, in subjects for whom biopsy samples were available or who came to autopsy after receiving a PET amyloid scan, support the relationship between PET amyloid imaging results and cortical neuritic plaque density (Clark 2011, 2012; Leinonen, 2008; Sojkova, 2011; Kantarci, 2011; Burack, 2010). The largest of these studies (Clark 2012) demonstrated a high sensitivity and specificity for florbetapir PET to discriminate subjects with subsequent autopsy findings of no or sparse neuritic plaques (amyloid negative) from those with moderate to frequent plaques (amyloid positive).

The ability to image brain amyloid with compounds such as florbetapir is an important advance for diagnosis of neurological disease. An amyloid negative florbetapir PET scan indicates the absence of a hallmark pathology and is inconsistent with a diagnosis of AD. However, because amyloid is believed to accumulate very early in the disease process (Jack et al., 2010) and may be present in other diseases or in clinically normal elderly subjects (Sperling et al. 2011; Price and Morris, 1999), the density or distribution of amyloid in subjects with a positive scan is not associated with Alzheimer's disease severity, has not been established to predict rate of future deterioration and has not been established as a tool to predict or monitor response to therapy.

In contrast to A β neuritic plaques, the density and distribution of phosphorylated tau, aggregated in neurofibrillary tangles, increases with AD-related cognitive impairment and correlates with neurodegeneration (Dickson et al., 1997; Duyckaerts et al., 1987). Thus, a PET imaging agent that binds to phosphorylated tau has potential application as a biomarker for disease severity/neurodegeneration and may be useful both for selecting patients for therapy and for monitoring disease progression in therapeutic trials.

¹⁸F-AV-1451 (originally named [F-18]T807 by Siemens Molecular Imaging Biomarker Research group) has been developed as a positron emitting radiopharmaceutical for *in vivo* imaging of tau protein aggregates (Xia et al., 2013). Autoradiography results using tissue sections from human brains showed a strong signal in the grey matter of cortical slices from tau positive brains but weak or no binding in tau negative, A β positive, or tau and A β negative tissue. Scatchard analysis based on this heterogeneous autoradiography assay yielded an estimated K_d of 15nM. A saturation binding experiment using purified Paired Helical Fragment Tau isolated brains of AD patients yielded a K_d value of 0.7 nM.

AV-1451 was assessed in competitive binding assays against a panel of 72 of the most common central nervous system (CNS) targets and no clinically relevant inhibition was seen. AV-1451 was positive in the *in vitro* hERG assay; however, *in vivo* cardiovascular safety pharmacology assessments in dogs showed no evidence of QT prolongation at doses up to 50x the intended maximum human dose (MHD). Nonetheless, until

sufficient human cardiovascular safety data are available, initial clinical studies will exclude subjects with a history of risk factors for Torsades de Pointes and subjects taking drugs known to prolong the QT interval.

In vivo safety pharmacology studies were also conducted in rats to determine potential effects on the CNS and respiratory systems. In these studies no clinically relevant effects were reported at doses exceeding 100x the intended MHD. Additionally, non-radioactive AV-1451 has been tested in single and repeat-dose toxicology studies in rat and dog. In each of these studies the no observable adverse effect levels (NOAELs) were the highest doses tested (150x MHD for single, 50x MHD for repeat).

Potential genotoxicity of non-radioactive AV-1451 was tested in both *in vitro* and *in vivo* assays. In the *in vitro* assays, AV-1451 tested positive for potential genotoxicity. However, in the *in vivo* rat micronucleus assay at doses up to 750x MHD (scaled allometrically), AV-1451 showed no evidence of genotoxicity. The different results in the *in vitro* genotoxicity assays and the *in vivo* micronucleus study are likely related to differences in the exposure conditions encountered by the target cells in the different test systems. *In vivo*, AV-1451 is cleared rapidly; however, the *in vitro* experiments employ static, prolonged exposure of cells to high concentrations of the test article. While the *in vitro* data show the potential for genotoxicity, the *in vivo* data provide assurance that genotoxicity is unlikely to occur at clinically-relevant doses for human diagnostic studies.

¹⁸F-AV-1451 has been evaluated in two human studies under the exploratory IND (Chien, et. al). Adverse events reported have been mild and transient; none have been considered related to ¹⁸F-AV-1451 administration. Preliminary evaluation of the PET images suggest that ¹⁸F-AV-1451 is eliminated from normal brain yielding only a diffuse pattern of background activity (Figure 1), whereas a regionally-specific gray matter distribution is observed in subjects with high probability AD (Figure 2).

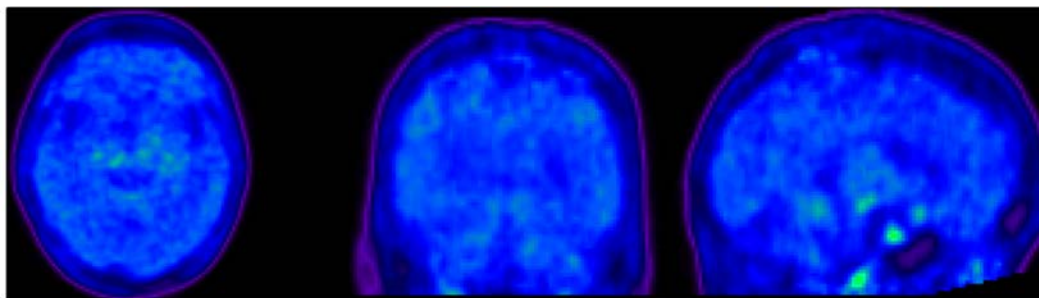


Figure 1: ██████████ control subject (MMSE = 29)

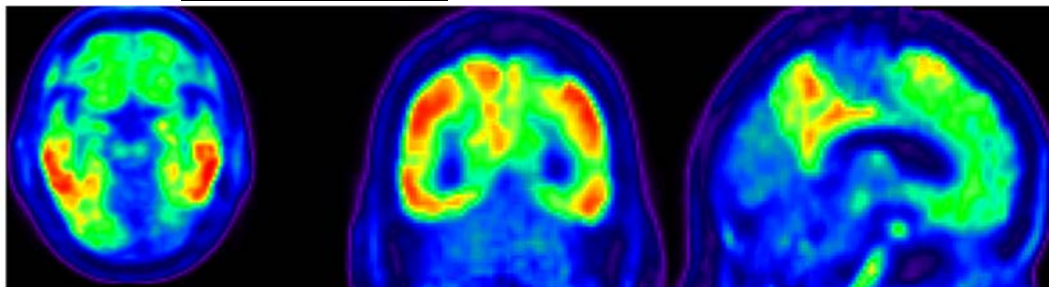


Figure 2: ██████████ AD subject (MMSE = 18)

Human dosimetry has been obtained in nine subjects. Generally, the radiotracer distribution was consistent among the subjects and showed rapid hepatobiliary clearance. There were three organs that received estimated doses higher than 0.05 mSv/MBq. The organ that received the largest estimated dose was the upper large intestinal wall (0.0962 ± 0.0134 mSv/MBq), followed by the small intestine and the liver. The Effective Dose was 0.0241 ± 0.0016 mSv/MBq. This results in an estimated Effective Dose of 8.92 mSv for an anticipated 370 MBq (10 mCi) injection and is comparable to the effective dose of approved ¹⁸F-labeled compounds such as fluorodeoxyglucose (FDG) and florbetapir F 18 injection.

The overarching goal of this protocol is to further investigate the spectrum of PET imaging results with ¹⁸F -AV-1451 in patients with cognitive decline and healthy controls. To accomplish this goal, the protocol will investigate ¹⁸F-AV-1451 results in younger and older controls and patients with cognitive complaints ranging from mild cognitive impairment (MCI) to mild and moderate Alzheimer's disease (AD). Additionally, this protocol will investigate correlations between ¹⁸F-AV-1451 PET imaging and other biomarkers associated with AD and will test the relationship between ¹⁸F-AV-1451 PET imaging and cognitive decline over the 18 month study period.

2. TRIAL OBJECTIVES

This study will be conducted in two phases, an exploratory phase and a confirmatory/validation phase, which will have separate subjects and analyses. The first phase of this study will be comprised of a cross-sectional component and a longitudinal component. The second (confirmatory/validation) phase will focus on the relationship of baseline PET tau images to change in longitudinal clinical measure.

2.1. Exploratory Phase, Cross-sectional objectives:

The primary objective of the cross-sectional component is:

- To compare ¹⁸F-AV-1451 imaging results in subjects with AD to subjects with MCI and cognitively healthy older individuals

The secondary objective of the cross-sectional component is:

- To establish a database of cognitively healthy individuals to show the spectrum of ¹⁸F-AV-1451 imaging results in cognitively healthy individuals across a range of age strata

Exploratory objectives of the cross-sectional component are:

- To determine whether greater degrees of cognitive impairment correlate with higher ¹⁸F-AV-1451 uptake in subjects with an amyloid positive status
- To explore whether tests of specific cognitive domains correlate with regional ¹⁸F-AV-1451 uptake
- To explore the relationships between ¹⁸F-AV-1451 uptake and biomarkers of neurodegeneration and neurological disease (CSF markers including tau, phospho-tau and beta-amyloid (A β), genetic markers, PET amyloid imaging, and brain atrophy assessed by volumetric MRI)
- To expand the ¹⁸F-AV-1451 safety database

2.2. Exploratory Phase, Longitudinal objectives:

The primary objective of the first phase of the longitudinal component is:

- To assess the rate of change of tau deposition as measured by ¹⁸F-AV-1451 uptake over time.

The exploratory objectives of the first phase of the longitudinal component are:

- To explore associations between changes in ¹⁸F-AV-1451 uptake in the brain and clinical and functional measures, as well as, biomarkers of neurodegeneration and neurological disease (CSF markers including tau, phospho-tau and beta-amyloid (A β), genetic markers, PET amyloid imaging, and brain atrophy assessed by volumetric MRI)
- To expand the ¹⁸F-AV-1451 safety database

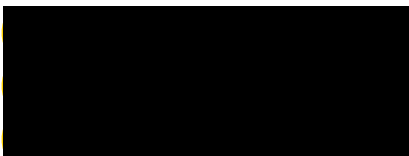
2.3. Confirmatory Phase, Longitudinal objectives:

The second phase of the study is designed to provide independent validation of the relationships observed in the exploratory analyses of the first phase. In particular, the goal of the second phase is to confirm the relationship between ¹⁸F-AV-1451 uptake in the brain as measured by PET and the subsequent rate of cognitive decline observed over longitudinal follow up.

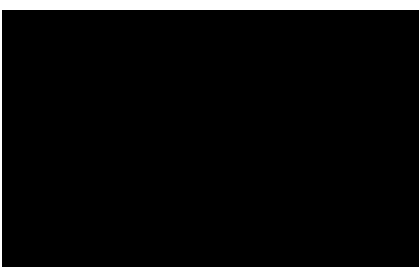
3. SPONSOR, INVESTIGATOR(S) AND OTHER PARTICIPANTS

The trial is sponsored by:

Avid Radiopharmaceuticals, Inc.



The medical contact is:

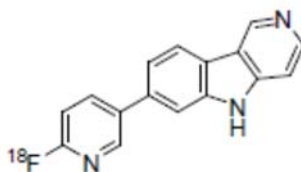


Approximately 30 centers in the United States will participate.

4. TEST DRUG AND CONTROL AGENTS

4.1. Descriptive Name: ¹⁸F AV-1451

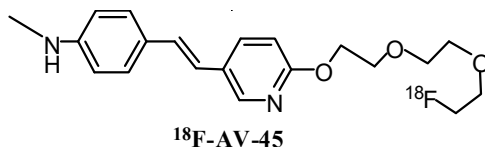
7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole



MW = 262.27 amu

4.2. Descriptive Name: Florbetapir F 18

4-[(1E)-2-[6-[2-[2-[2-(fluoro-¹⁸F)ethoxy]ethoxy]ethoxy]-3-pyridinyl]ethenyl]-N-methyl-benzenamine



MW= 359.4 amu

4.3. Radioactive Labeling

The compounds are labeled with [¹⁸F] fluorine that decays by positron (β^+) 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.

4.4. Decay Characteristics

The time course of radioactive decay for Fluorine [¹⁸F] is shown below

Min.	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

Physical decay chart for Fluorine [¹⁸F]. Half-life = 109.77 min.

4.5. Formulation and Dose Florbetapir F 18 Injection

Drug Product is formulated in 10% v/v ethanol, USP, 0.45% sodium ascorbate, USP, in 0.9% sodium chloride injection, USP. Subjects will receive a single IV administration of approximately 370 MBq (10 mCi) of Florbetapir F 18 Injection immediately prior to imaging. The mass dose of florbetapir in each human dose will be $\leq 50 \mu\text{g}$ (0.14 μmol) per 10 mCi dose in total volume not exceeding 10 mL. Florbetapir F 18 Injection expires at 10 hours post End-of-Synthesis (EOS) or when either the strength or specific activity shelf-life specifications (Not less than (NLT) 37 MBq/mL (1 mCi/ml) or NLT 7.4 MBq/ μg (0.2mCi/ μg), respectively) are met, whichever is soonest.

Florbetapir F 18 Injection will be supplied from manufacturing facilities approved for commercial distribution under NDA 202-008.

4.6. Formulation and Dose ^{18}F -AV-1451 Injection

^{18}F -AV-1451 Injection is a clear solution containing ^{18}F -AV-1451 (drug substance) formulated for intravenous bolus administration. Depending on the manufacturer, ^{18}F -AV-1451 Injection will be formulated in:

- aqueous 21 mM sodium phosphate solution containing up to 10% (v/v) ethanol, or
- a solution containing 10% (v/v) ethanol, USP in 0.9% sodium chloride injection, USP.

Drug product of either formulation is manufactured to meet one common set of specifications.

The expiration time and date of ^{18}F -AV-1451 Injection are provided on the outer label of each dose based on specific activity or strength. ^{18}F -AV-1451 Injection should be stored at room temperature.

4.7. Packaging Florbetapir F 18 Injection

Unit doses of Drug Product may be contained in a sterile, apyrogenic 10, 30 or 50 mL clear Type I Borosilicate glass serum vial closed with a 20 mm Fluro Tec®-coated 4432/50-B2-40 gray elastomeric closure sealed with a 20 mm aluminum crimp seal, manufactured by Allergy Laboratories or may be contained in 2 mL, 5 mL, or 10 mL sterile apyrogenic NORM-JECT® polypropylene/high-density polyethylene syringes.

4.8. Packaging ^{18}F -AV-1451 Injection

Each package of ^{18}F -AV-1451 Injection includes a sterile apyrogenic sealed glass vial or sterile apyrogenic syringe containing ^{18}F -AV-1451 Injection, a surrounding protective lead shield canister, and an outside delivery case.

4.9. Storage and Handling Florbetapir F 18 Injection

Florbetapir F 18 Injection is stored at 25°C; excursions permitted to 15-30°C. The product does not contain a preservative. Florbetapir F 18 Injection should be stored within the original container or equivalent radiation shielding. Florbetapir F 18 Injection must not be diluted.

4.10. Storage and Handling ^{18}F -AV-1451 Injection

^{18}F -AV-1451 Injection is stored at room temperature. ^{18}F -AV-1451 Injection should be stored within the original container or equivalent radiation shielding. ^{18}F -AV-1451 Injection must not be diluted.

5. INVESTIGATIONAL PLAN

5.1. Overall Design and Plan of Trial

This is a phase 2 cross-sectional and longitudinal observational study that will evaluate imaging characteristics of ¹⁸F-AV-1451 in control subjects and patients with MCI and AD. This study will be conducted in two phases, an exploratory/hypothesis generating phase and a confirmatory/validation phase, which will have separate subjects and analyses. Approximately 230 subjects will be enrolled in the Exploratory Phase of the study: 80 cognitively healthy volunteers, 80 subjects with MCI, 70 subjects with AD. Approximately 20 cognitively healthy volunteers will be ≥ 20 to ≤ 40 years of age. Approximately 60 cognitively healthy volunteers will be ≥ 50 years of age and will be distributed across age deciles (50-59, 60-69, 70-79 and ≥ 80). Approximately 150 subjects with cognitive impairment will be enrolled in the Confirmatory Phase.

All subjects will provide informed consent before starting any study procedures.

For both the Exploratory and Confirmatory Phases, screening assessments may take place over several days and will include demographic information, cognitive testing, safety assessment, and MRI, including both volumetric and standard clinical sequences. Raters administering the cognitive testing will be blinded to the ¹⁸F-AV-1451 scans for subjects in the Confirmatory Cohort. Subjects who qualify for the study will undergo both a florbetapir F 18 PET imaging session and an ¹⁸F-AV-1451 PET imaging session. Some subjects, who are ≥ 50 years of age, in the Exploratory Phase will have the option to participate in cerebrospinal fluid (CSF) collection by lumbar puncture (LP).

Subjects who are ≥ 50 years of age will return for follow-up visits at 9 (+/-2) months and 18 (+/-2) months following the initial ¹⁸F-AV-1451 scan. Cognitive assessments and updates to concomitant medications and medical history will be collected at each follow-up visit. Subjects in the Exploratory Phase will also have follow up ¹⁸F-AV-1451 scans and MRI, including both volumetric and standard clinical sequences. A sub-set of subjects in the Exploratory Phase may have the option to have an additional resting state functional (rsf)MRI sequence scan in addition to the volumetric and standard clinical sequences at both the screening MRI and follow-up MRIs. All follow-up procedures should be collected within the specified visit window (See Section 7.1.4). Subjects or their designated decision maker will be contacted by phone at 5 and 14 months following the initial ¹⁸F-AV-1451 scan to collect updated concomitant medications and medical history.

Avid personnel will be blinded to the Confirmatory Phase longitudinal cognitive data. Avid personnel will also remain blinded to the PET scans (both florbetapir and ¹⁸F-AV-1451) performed on subjects in the Confirmatory Phase with the exception of periodic quality assurance (QA) assessments of a random subset of image data (not to exceed 20% unless issues identified that warrant additional review). These QA reviews will serve to ensure image quality and data integrity for the scans collected and managed by the imaging core laboratory. Avid staff performing the PET scan QA assessment will not be aware of diagnostic group or cognitive test scores for the subjects/images being reviewed.

Florbetapir F 18 PET Imaging Session:

For the florbetapir F 18 PET imaging session, an intravenous catheter will be placed for IV administration of Florbetapir F 18 Injection. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of Florbetapir F 18 Injection followed by a saline flush. At approximately 50 minutes following injection, a continuous 10-minute brain scan (2 acquisitions of 5 minute duration) will begin.

Adverse events will be continuously monitored during the florbetapir F 18 PET imaging session. A physician or physician designee must evaluate the subject for adverse events prior to injection and prior to discharge from the imaging center. Subjects who experience an adverse event will not be discharged from the imaging center until the event has resolved or stabilized.

A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days of the post-injection of florbetapir F 18, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

¹⁸F-AV-1451 PET Imaging Session(s):

For the ¹⁸F-AV-1451 PET imaging session(s), an intravenous catheter will be placed for IV administration of ¹⁸F-AV-1451 Injection. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of ¹⁸F-AV-1451 Injection followed by a saline flush. At approximately 80 minutes post dose, a continuous 20-minute brain scan (4 acquisitions of 5-minute duration) will be obtained. If at any point during the imaging session it is determined that the subject is not able to continue, or that it is not in the best interest of the subject to continue, imaging will be discontinued. The image data that has been collected up to that point will be analyzed. Clinical laboratory tests will be obtained prior to injection and upon completion of each imaging session. Adverse events will be monitored continuously during the imaging session. Subjects who experience any adverse event during an imaging session will not be discharged until the event has resolved or stabilized.

A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

5.2. Planned Dosage and Duration of Treatment**5.2.1. Dosage and Administration****Florbetapir F 18:**

Subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of Florbetapir F 18 Injection.

¹⁸F-AV-1451:

All subjects will receive a single IV bolus administration target dose of 370 MBq (10 mCi) of ¹⁸F-AV-1451 Injection.

5.2.2. Rationale for Dosages

This trial is designed to evaluate the brain tau protein imaging properties and safety of ¹⁸F-AV-1451 to be used in subjects with cognitive impairment and healthy volunteers. ¹⁸F-AV-1451 will be administered IV in a radioactive target dose of 370 MBq with a maximum human mass dose (MHD) limited to 20 µg of compound by weight. This dose is 150 fold lower than the NOAEL observed in the rat single dose toxicity study and is 50 fold lower than the NOAEL observed in the rat and dog repeat dose toxicity studies.

Human dosimetry has been obtained in nine subjects. The results estimated an Effective Dose of 8.92 mSv for an anticipated 370 MBq (10 mCi) injection and is comparable to the effective dose of approved ¹⁸F-labeled compounds such as FDG and Florbetapir F 18 Injection.

The proposed dose has been shown to have acceptable image quality in preliminary human studies. No treatment related adverse events have been reported using this regimen.

5.3. Selection of Subjects**5.3.1. Inclusion Criteria**

Subjects who meet all of the following criteria are eligible to enroll in this trial as cognitively healthy volunteers:

1. Male or female subjects ≥ 20 to ≤ 40 years of age
(n = approximately 20)
-OR-
Male or female subjects ≥ 50 years of age
(n = approximately 60)
2. MMSE ≥ 29
3. No significant history of cognitive impairment
4. Can tolerate PET imaging procedures
5. Can tolerate MRI scan procedures, and
6. Subjects who signed an IRB approved informed consent prior to any study procedures.

Subjects who meet all of the following criteria are eligible to enroll in the arm of this trial reserved for patients with MCI:

1. Male or female subjects ≥ 50 years of age

2. MMSE \geq 24
3. Have MCI consistent with NIA-Alzheimer's Association working group's diagnostic guidelines for AD: Alzheimer's Dementia 7:270-9, 2011 (Albert 2011), including the following:
 - a. Have cognitive decline verified by the study physician.
 - b. Evidence of objective impairment in one or more cognitive domains, with supporting evidence from objective testing if available,
 - c. Preservation of independence in functional abilities,
 - d. Not demented
4. Have a study partner who has significant interaction with the subject and can report on the subject's activities of daily living
5. Can tolerate PET imaging procedures
6. Can tolerate MRI scan procedures, and
7. Ability to provide informed consent for study procedures (If the patient is ineligible to give informed consent, based on local standards, the patient's legal representative may consent on behalf of the patient but the patient must still confirm assent. This person may serve as the study partner as well).

Subjects who meet all of the following criteria are eligible to enroll in the arm of this trial reserved for patients with AD:

1. Male or female subjects \geq 50 years of age
2. MMSE $>$ 10
 - a. Approximately 60 subjects with an MMSE \geq 20
 - b. Approximately 10 subjects with an MMSE $>$ 10 and $<$ 20
3. Subjects with possible or probable AD based on the NIA-Alzheimer's Association working group's diagnostic guidelines for AD: Alzheimer's Dementia 7:263-9, 2011
4. Have a study partner who has significant interaction with the subject and can report on the subject's activities of daily living
5. Can tolerate PET imaging procedures
6. Can tolerate MRI scan procedures, and
7. Ability to provide informed consent for study procedures (If the patient is ineligible to give informed consent, based on local standards, the patient's legal representative may consent on behalf of the patient but the patient must still confirm assent. This person may serve as the study partner as well).

Subjects who meet all of the following criteria are eligible to enroll in the second phase of this trial: Confirmatory Cohort:

1. Male or female subjects \geq 50 years of age (n = approximately 150)

2. Cognitively impaired subjects (MCI or dementia with a suspected neurodegenerative cause) with an MMSE ≥ 20 and ≤ 27 . (For the purpose of ensuring a distribution of disease severity, a target of at least 1/3 of the enrolled subjects will have dementia).
3. Have a study partner who has significant interaction with the subject and can report on the subject's activities of daily living
4. Can tolerate PET imaging procedures
5. Can tolerate MRI scan procedures, and
6. Ability to provide informed consent for study procedures (If the patient is ineligible to give informed consent, based on local standards, the patient's legal representative may consent on behalf of the patient but the patient must still confirm assent. This person may serve as the study partner as well).

5.3.2. Exclusion Criteria

Subjects will be excluded from enrollment if they:

1. Have current clinically significant psychiatric disease. Subjects with behavior dysfunction in AD may be entered only after discussion and with approval of the sponsor. The investigator should carefully consider whether subjects with behavior dysfunction in AD will be able to complete the imaging session
2. Have evidence of structural abnormalities such as major stroke or mass on MRI that is likely to interfere with interpretation of a PET scan on MRI
3. Have a history of moderate or severe traumatic brain injury (TBI) by OSU TBI-ID method or evidence of brain injury by MRI or CT imaging
4. Are claustrophobic or otherwise unable to tolerate the imaging procedure
5. Have current clinically significant cardiovascular disease or clinically significant abnormalities on screening ECG (including but not limited to Fridericia's corrected QT (QTcF) >450 msec)
6. A history of additional risk factors for Torsades de Pointes (TdP) (e.g., heart failure, hypokalemia, family history of Long QT syndrome) or are taking drugs that are known to cause QT-prolongation (a list of prohibited and discouraged medications is provided by the Sponsor)
7. Have a current clinically significant infectious disease, endocrine or metabolic disease, pulmonary, renal or hepatic impairment, or cancer that the investigator believes would affect study participation or scan results
8. Have a history of significant or ongoing alcohol abuse or substance abuse or dependence
9. Are females of childbearing potential who are not surgically sterile, not refraining from sexual activity or not using reliable methods of contraception. Females of childbearing potential must not be pregnant (negative serum β -HCG at the time of screening and negative urine β -HCG within 24 hours prior to injection) or

- breastfeeding at screening. Females must agree to avoid becoming pregnant, and both females and males must agree to refrain from sexual activity or to use reliable contraceptive methods for 90 days following administration of ¹⁸F-AV-1451 Injection
10. Have had a non-study related radiopharmaceutical imaging or treatment procedure within 7 days prior to the ¹⁸F-AV-1451 or florbetapir F18 imaging session
 11. Are receiving any investigational medications, or have participated in a trial with investigational medications within the last 30 days
 12. In the opinion of the investigator, are otherwise unsuitable for a study of this type.

5.4. Prior and Concomitant Therapy

Except as noted below, all medications (prescription or over-the-counter) that have been started prior to screening may be continued during the course of the trial. 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 in the case record form on the Concomitant Medication Page of the Case Record Form (CRF).

Investigators must discuss with the sponsor and carefully consider whether subjects requiring psychotropic medications will be able to complete the imaging session.

Subjects who are taking drugs that are known to cause QT-prolongation may not be enrolled in the study (a list of prohibited and discouraged medications is provided by the Sponsor).

Subjects may be permitted to enroll in a clinical trial with a potential disease modifying (anti-tau or anti-amyloid) investigational medication after discussion with the sponsor.

5.5. Removal of Subjects from Trial

Subjects 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.

Subjects 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.

5.6. Premature Termination of Trial/Closure of Center

The sponsor may discontinue the trial at any time. Reasons for discontinuation of the trial 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 or inability 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 the safety of study subjects.

6. WARNINGS/PRECAUTIONS

The most up-to-date and complete information regarding the use of ¹⁸F-AV-1451 Injection can be found in the investigator's brochure.

In brief, ¹⁸F-AV-1451 Injection is an experimental imaging agent that will be used at relatively low (tracer) doses. However, because relatively little toxicological evaluation has been completed, and because ¹⁸F-AV-1451 Injection is in the early stages of clinical investigation, it is recommended that subjects receiving ¹⁸F-AV-1451 Injection be followed closely by means of adverse event reporting, vital signs, ECGs, and laboratory tests.

There are no data on the effects of ¹⁸F-AV-1451 Injection in human perinatal development. For this reason, females must avoid becoming pregnant. Both females and males must use adequate contraceptive methods for 90 days after administration of ¹⁸F-AV-1451 Injection. ¹⁸F-AV-1451 Injection must not be administered to females who are pregnant or lactating.

7. PROCEDURES AND METHODS

7.1. Assessment Periods

See Section 11.2, Trial Flow Charts.

This study will be comprised of a cross-sectional component and a longitudinal component. Subjects in both the Exploratory Phase and Confirmatory Phase will have screening visit(s), a florbetapir F 18 PET imaging visit, a ¹⁸F-AV-1451 PET imaging visit, and follow-up phone calls after each imaging visit. Subjects who are ≥ 50 years old will return for follow-up visits at 9 (+/-2) and 18 (+/-2) months following the initial ¹⁸F-AV-1451 scan. Cognitive assessments and updates to concomitant medications and medical history will be collected at each follow-up visit. Subjects in the Exploratory Phase will also have follow-up ¹⁸F-AV-1451 scans and MRI.

7.1.1. Screening and Baseline Visit:

Screening may take place over several days. All screening assessments should be performed within 30 days of the initial ¹⁸F-AV-1451 PET imaging session.

Screening assessments will include:

- Informed consent;

- Demographics (age, gender, race, ethnicity, education, alcohol, drug use, and smoking);
- Medical history, physical and neurological exam, concomitant medications;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of neurologic disease) for cognitively impaired subjects;
- Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID);
- Mini Mental State Exam (MMSE);
- Safety assessments: Vital signs (pulse rate, respiratory rate, supine blood pressure, height and weight), ECG, safety labs(hematology, chemistry, and urinalysis);
- Serum beta-hCG test (for females of childbearing potential defined as pre-menopausal or less than 2 years post-menopausal and not surgically sterile);
- MRI imaging including standard clinical sequences and volumetric MRI;
- A physician will see the patient during the screening visit.

Baseline assessments may be performed at the screening visit or +/- 30 days of the initial ¹⁸F-AV-1451 Imaging Visit. Raters administering the MMSE and baseline assessments described below will be blinded to the ¹⁸F-AV-1451 scans for subjects in the Confirmatory Cohort.

Baseline assessments will include:

- Alzheimer's Disease Assessment Scale- Cognitive subscale (ADAS-Cog₁₁);
- Neuropsychological test battery (Digit Symbol Substitution Test (DSST), Digit span forward and backward, Trail Making A and B, Logical Memory Test, Immediate and Delayed Recall Story A, Animal list generation, Boston Naming Test (BNT) (30 item), American National Adult Reading Test (ANART), Clock Drawing Test, Benton Judgment of Line Orientation test);
- Subjects in the Confirmatory Cohort will also be administered the Clinical Dementia Rating (CDR) Scale;
- Pfeffer Functional Activities Questionnaire (FAQ). For the MCI and AD groups only.

7.1.2. Optional Cerebrospinal fluid (CSF) collection by Lumbar Puncture (LP) (A β , p-tau, t-tau); Exploratory Phase only

Some subjects (depending on site participation) who are ≥ 50 years of age who qualify for the study will be offered to consent for optional CSF collection by LP. The LP should be performed at least 48 hours apart from the PET imaging sessions and should be performed within +/- 60 days of the initial ¹⁸F-AV-1451 Imaging Visit. Each LP will be done by a qualified physician who is experienced in performing the procedure. Subjects,

or their designated decision maker, will call the investigator to report any adverse events associated with the LP procedure.

7.1.3. Initial PET Imaging Visits:

Subjects who qualify will have a florbetapir F 18 PET imaging session and their initial ¹⁸F-AV-1451 PET imaging session. The imaging sessions must be performed at least 48 hours apart, but not more than 60 days apart. The order of the scans is interchangeable.

Florbetapir F 18 PET Imaging Session

- For women of childbearing potential, a negative urine pregnancy test must be obtained within 24 hours prior to injection;
- A physician or physician designee must see the subject prior to administration of Florbetapir F 18 Injection to determine if they are still suitable to undergo the scan;
- Vital signs will be taken (pulse rate, respiratory rate, supine blood pressure, and weight) immediately prior to injection of florbetapir F 18;
- Subjects will receive a single IV bolus injection of approximately 370 MBq (10 mCi) +10% of florbetapir F 18 followed by a saline flush. A 10-minute(2 acquisitions of 5 minute duration) continuous, dynamic PET brain scan will begin approximately 50 minutes following the dose administration;
- A physician or physician designee will see the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge;
- A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

¹⁸F-AV-1451 PET Imaging Session: Raters administering the MMSE and baseline assessments will be blinded to the ¹⁸F-AV-1451 PET scan for subjects in the Confirmatory Cohort.

- A physician must see the subject prior to administration of ¹⁸F-AV-1451 Injection to determine if they are still suitable to undergo the scan;
- For women of childbearing potential, a negative urine pregnancy test must be obtained;
- Vital signs will be taken at the following time points:
 - immediately prior to administration of ¹⁸F-AV-1451 Injection
 - within 5 minutes after completion of injection of ¹⁸F- AV-1451 Injection
 - after completion of the PET scan, prior to discharge;
- ECGs will be taken at the following time points:

- Two will be taken approximately 5 minutes apart immediately prior to (within approximately 10 minutes) ¹⁸F-AV-1451 Injection administration
- One will be taken within five minutes after completion of injection
- One will be taken after completion of the PET scan, prior to discharge;
- Blood and urine samples will be collected for safety labs prior to administration of ¹⁸F-AV-1451 Injection and after completion of the PET scan prior to discharge;
- Blood will be collected for evaluation of ApoE genotype;
- Blood will be collected for storage and genetic analysis (participant may opt out) ;
- Subjects will receive a single IV bolus injection of approximately 370 MBq (10 mCi) +10% of ¹⁸F-AV-1451 Injection followed by a saline flush. At approximately 80 minutes post dose, a continuous 20-minute brain scan (4 acquisitions of 5 minute duration) will be obtained.);
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected;
- The subject will be requested to void after completion of the PET scan;
- Adverse events will be continuously monitored during the ¹⁸F-AV-1451 study imaging session; Subjects who experience an adverse event will not be discharged from the imaging center until the event has resolved or stabilized;
- A physician will see the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge; and
- A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

Longitudinal Visit Procedures

The longitudinal component will consist of the following sequence of activities:

7.1.4. First and Second Longitudinal Follow-up Visits

Exploratory Phase: The first and second follow-up visits will consist of PET scan procedures, an MRI, cognitive assessments and updated medical history and concomitant medications. The first follow-up scan will occur 9 (+/-2) months following the subject's initial ¹⁸F-AV-1451 scan. The second follow up scan will occur 18 (+/-2) months following the initial ¹⁸F-AV-1451 scan. The cognitive assessments and MRIs should be performed +/- 30 days of each corresponding ¹⁸F-AV-1451 PET imaging visit and within

the 9 (+/-2) months window. The cognitive assessments and MRI should take place in the same 30 day window.

Confirmatory Phase Cohort: The first and second follow-up visits will consist of cognitive assessments and updated medical history and concomitant medications. The first follow-up visit will occur 9 (+/-2) months following the subject's initial ¹⁸F-AV-1451 scan. The second follow-up visit will occur 18 (+/-2) months following the initial ¹⁸F-AV-1451 scan.

Cognitive Assessments: Raters administering the below assessments will be blinded to the ¹⁸F-AV-1451 scans for subjects in the Confirmatory Cohort

- Mini Mental State Exam (MMSE);
- Alzheimer's Disease Assessment Scale- Cognitive subscale (ADAS-Cog₁₁);
- Neuropsychological test battery (Digit Symbol Substitution Test (DSST), Digit span forward and backward ,Trail Making A and B, Logical Memory Test, Immediate and Delayed Recall Story A , Animal list generation, Boston Naming Test (BNT) (30 item), American National Adult Reading Test (ANART), Clock Drawing Test, Benton Judgment of Line Orientation test);
- Clinical Dementia Rating (CDR) Scale; For the MCI and AD groups only.
- Pfeffer Functional Activities Questionnaire (FAQ). For the MCI and AD groups only.

Magnetic Resonance Imaging (MRI) (for Exploratory Phase cohort only)

MRI, including both volumetric and standard clinical sequences, will be obtained at the first and second follow-up visits.

¹⁸F-AV-1451 PET Imaging Session (for Exploratory Phase cohort only)

The first follow-up scan will occur 9 (+/-2) months following the subject's initial ¹⁸F-AV-1451 scan. The second follow up scan will occur 18 (+/-2) months following the initial ¹⁸F-AV-1451 scan. Procedures for the longitudinal follow-up scans will be identical to the initial scan:

- A physician must see the subject prior to administration of ¹⁸F-AV-1451 Injection to determine if they are still suitable to undergo the scan;
- Updated medical history and concomitant medications;
- For women of childbearing potential, a negative urine pregnancy test must be obtained;
- Vital signs will be taken at the following time points:
 - immediately prior to administration of ¹⁸F-AV-1451 Injection
 - within 5 minutes after completion of injection of ¹⁸F- AV-1451 Injection
 - after completion of the PET scan prior to discharge;
- ECGs will be taken at the following time points:

- Two will be taken approximately 5 minutes apart immediately prior to (within approximately 10 minutes) ¹⁸F-AV-1451 Injection administration
- One will be taken within five minutes after completion of injection
- One will be taken after completion of the PET scan prior to discharge;
- Blood and urine samples will be collected for safety labs prior to administration of ¹⁸F-AV-1451 Injection and after completion of the PET scan prior to discharge;
- Subjects will receive a single IV bolus injection of approximately (370 MBq) 10 mCi (+10%) of ¹⁸F-AV-1451 Injection followed by a saline flush. At approximately 80 minutes post dose, a continuous 20-minute brain scan (4 acquisition of 5-minute duration).
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected;
- The subject will be requested to void after completion of the PET scan;
- Adverse events will be continuously monitored during the ¹⁸F-AV-1451 study imaging session; Subjects who experience an adverse event will not be discharged from the imaging center until the event has resolved or stabilized;
- A physician will see the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge; and
- A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

7.1.5. Longitudinal Follow-Up Phone Calls

Subjects or their designated decision makers will be contacted by phone at 5 and 14 months following the initial ¹⁸F-AV-1451 scan to collect updated concomitant medications and medical history.

7.2. Observations and Measurements

Informed Consent

Potential subjects and legally authorized representatives, if applicable, will be allowed to read a written informed consent form. The principal investigator or designee will explain all study procedures, risks, and alternative therapies to subject. The subject 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 subject or legally authorized representative.

All informed consent forms must be approved by Avid or designee, and by the appropriate Institutional Review Board (IRB) prior to use.

Medical History, Neurologic Disease History

The investigator or designee will obtain a case history at the screening visit.

- Relevant demographic information
- Review of body systems
- Social history
- Medical and surgical history
- Concurrent medications
- Neurologic Disease history (month and year of symptom onset, month and year of diagnosis, family history of neurologic disease)

Whenever possible, the medical history will be confirmed by medical records.

Physical Examination

A complete physical examination will be conducted at the screening visit. Clinically significant changes from screening will be recorded as adverse events for the relevant study period.

Neurological Examination

A neurological examination will be performed at the screening visit to evaluate cranial nerves, gait, sensory, and motor function, coordination and tendon reflexes. The investigator is to look for these specific signs:

- Pyramidal signs (plantar extension reflex, Achilles tendon clonus);
- Extrapyramidal signs (rigidity, wrist cogwheel phenomena, involuntary movements); and
- Myoclonus.

MRI

MRI, including both volumetric and standard clinical sequences will be obtained. The MRI sequences and acquisition parameters will be described in a separate document. If a comparable MRI has been performed within the last six months, for the screening MRI, and an electronic copy of the images is available for submission, it should be discussed with the sponsor whether the MRI need not be repeated.

A sub-set of subjects in the Exploratory Phase may have the option to have a rsfMRI in addition to the volumetric and standard clinical sequences at both the screening MRI and follow-up MRIs.

Electronic copies of MRI scans will be submitted to Avid or designated imaging core lab.

Vital Signs

Vital signs (pulse rate, respiratory rate, supine blood pressure) will be taken at the following time points:

- Screening visit
- Florbetapir F18 Imaging Day
 - immediately prior to injection of florbetapir F 18
- ¹⁸F-AV-1451 Imaging Day
 - Immediately prior to the administration of ¹⁸F-AV-1451 Injection
 - Within 5 minutes after completion of injection of ¹⁸F-AV-1451 Injection
 - After the completion of imaging prior to discharge

Temperature will be obtained at the following time points:

- ¹⁸F-AV-1451 Imaging Day
 - Immediately prior to the administration of ¹⁸F-AV-1451 Injection
 - After the completion of imaging prior to discharge

Height and Weight

At both the screening and imaging visits body weight will be measured, lightly clothed.

Height will be measured at screening.

Electrocardiogram

A resting 12-lead electrocardiogram will be recorded at screening. At the ¹⁸F-AV -1451 imaging visits the ECGs will be taken at the following time points:

- Two ECGs will be taken at approximately 5 minutes apart immediately prior (within approximately 10 minutes) to ¹⁸F-AV-1451 Injection administration.
- One ECG will be taken immediately (within approximately five minutes) after completion of ¹⁸F-AV -1451 injection.
- One ECG will be taken after completion of the PET scan prior to discharge.

Clinical Laboratory Tests

Clinical laboratory evaluation will be performed at screening, on imaging day: prior to administration of ¹⁸F-AV-1451 Injection, and after completion of ¹⁸F-AV-1451 imaging.

Tests will include:

- **Hematology** (5 mL EDTA): hemoglobin, hematocrit, RBC, WBC, MCH, MCHC, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelets, morphology, MCV, and RBC morphology.
- **Chemistry** (6 mL blood): total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), urea nitrogen, creatinine, glucose, uric acid, calcium, phosphorus, total protein, albumin, total cholesterol, triglycerides, sodium, potassium, bicarbonate, chloride, magnesium, globulin, GGT.

- **Urinalysis** (10 mL, urine): Samples will be used to assess glucose, RBC, WBC, specific gravity, pH, protein, ketones, urobilinogen, blood, nitrite, microscopic, color, bilirubin, casts, epithelial cells, leukocyte, esterase, and bacteria.
- **ApoE Genotyping** (10 mL, blood) will be performed at the initial ¹⁸F-AV-1451 imaging session for those subjects whose ApoE results are unknown.

Genetic Samples

A one-time blood collection (10 mL, blood) will be performed on the day of the initial ¹⁸F-AV-1451 imaging session for genetic analysis. Where local regulations allow, samples will be stored and analysis may be performed on genetic variants thought to play a role in dementia or related diseases. Samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Samples will be identified by the patient number and stored for up to 15 years after the last patient visit for the study at a facility selected by the sponsor. The sample and any data generated from it can only be linked back to the patient by investigator-site personnel. Subjects may opt out of participation.

Pregnancy Testing

- **Serum beta hCG, qualitative:** performed at screening for females of childbearing potential who are not surgically sterile. A serum pregnancy test may also be obtained prior to injection at the Imaging Visit if required by the local site.
- **Urine beta hCG:** performed at both the ¹⁸F-AV-1451 and florbetapir F 18 imaging visit(s) prior to injection for females of childbearing potential (defined as pre-menopausal, less than 2 years post-menopausal or not surgically sterile).

Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID)

Tau pathology can be associated with Traumatic Brain Injury (TBI), therefore the OSU TBI-ID (Corrigan and Bogner 2007) short version will be used to screen for a history of traumatic brain injury. It is the briefest version that still provides several summary indices on which the original version was validated. To shorten the instrument, TBIs resulting in loss of consciousness are emphasized over less severe injuries.

Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975) is a brief instrument used to assess cognitive function in elderly patients. The instrument is divided into 2 sections. The first section measures orientation, memory, and attention. The maximum score for the first section is 21. The second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures. The maximum score for the second section is 9. The range for the total MMSE score is 0 to 30.

Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog 11)

The ADAS (ADAS-Cog; Rosen et al. 1984) was designed to assess the severity of the dysfunction in the cognitive and noncognitive behaviors characteristic of persons with AD. The cognitive subscale of the ADAS, the ADAS-Cog₁₁, consists of 11 items assessing areas of function most typically impaired in AD: orientation, verbal memory, language, and praxis. The scale ranges from 0 to 70, with higher scores indicating greater disease severity.

Digit Symbol Substitution Test (DSST)

The DSST (Wechsler Adult Intelligence Scale F Revised, 1981) is a paper test of psychomotor performance in which the subject is given a key of numbers and matching symbols and a test section with numbers and empty boxes. Under each number the subject should write down the corresponding symbol as fast as possible. The score is the number of correct number-symbol matches made within the allowed time (90 seconds). The strategy to solve the DSST consists of sequential encoding and retrieval of numbers and corresponding symbols. Incidental memory, visuo-motor coordination, perceptual organization, and selective attention are key factors that determine the final score (Wechsler Adult Intelligence Scale F Revised, 1981). The ability to sort out irrelevant information (e.g., symbols that may look alike) also impacts performance. This test has high test-retest reliability (Matarazzo and Herman, 1984).

Digit span forward and backward (Wechsler Memory Scale-Revised (WMS-R))

Digit Span is composed of two tasks administered independently of each other: Digits Forward and Digits Backward. On both tasks, the examiner reads a series of number sequences to the subject. For each Digits Forward item, the subject is required to repeat the number sequence in the same order as presented. For Digits Backward, the subject is required to repeat the number sequence in the reverse order.

Trail Making A and B

The trail making test (Reitan and Wolfson, 1985) is a test of executive function. Part A consists of 25 circles numbered 1 through 25 distributed over a sheet of paper. The subject is instructed to connect the circles by drawing a line as quickly as possible in ascending numerical order. Part B consists of 25 circles containing either numbers (1 through 13) or letters (A-L). The subject is instructed to connect the circles while alternating between numbers and letters in ascending order. The subject is timed. The time to complete Part A is a 150 second maximum and Part B is a 300 second maximum. Testing is stopped if the maximum time is reached.

Logical Memory Test, Immediate and Delayed Recall, Story A (WMS-R)

The logical memory test (Wechsler D. 1987) assesses the ability to recall a short story. Subjects are read a story and asked to recall the story immediately and after a delay.

Animal list generation

The animal list generation (Morris et al. 1989) is used to measure verbal fluency. The subject is asked to name as many animals as possible in 60 seconds.

Boston Naming Test (BNT) (30 item)

The 30 item Boston Naming Test (Kaplan, et al. 1983) is a measure of the ability to orally label 30 line drawings of objects. The objects are presented to the subject in order of frequency, from most frequent to least frequent.

American National Adult Reading Test (ANART)

ANART (Grober and Sliwinski 1991) is a measure for estimating premorbid verbal intelligence. The subject is presented with a word list and asked to pronounce the words.

Clock drawing test

The clock drawing test (Goodglass and Kaplan 1983) has two components: a command condition and a copy condition. In the command condition, the subject draws a clock according to verbal instructions. In the copy condition, the subject copies a model clock drawn at the top of a form.

Judgment of Line Orientation Test (JOLO)

The JOLO (Benton 1978) is a non-motor measure of visual perceptual ability where there is no time demand. The task asks subjects to match two lines by their angle of orientation to a test set of lines presented below the stimulus lines.

Pfeffer Functional Activities Questionnaire (FAQ), (Pfeffer et al. 1982)

Functional status is conceptualized as the “ability to perform self-care, self- maintenance and physical activities.” FAQ was developed to assess instrumental activities of daily living involving higher level functional skills such as shopping alone, writing checks, remembering appointments..etc. FAQ asks informant to rate patient’s ability using the following scoring system: Dependent = 3; Requires assistance = 2; Has difficulty but does by self = 1; Normal = 0; Never did [the activity] but could do now = 0; Never did and would have difficulty now = 1 The sum scores ranges from 0-30.

Clinical Dementia Rating (CDR) Scale (Berg, 1988)

The CDR examines 6 categories of cognitive functioning domains. Each domain is scored on a scale ranging from 0 to 3 (including 0.5). A global rating of dementia can be generated from the domain scores. A CDR Sum of Boxes can be generated from the total across domains.

Physician Visit

A physician must see the subject at screening, at baseline, prior to drug administration and at study end, prior to discharge from both the ¹⁸F-AV-1451 and florbetapir F 18 imaging sessions. At this time, the physician should review all safety data and briefly examine/query the subject regarding potential adverse events or other treatment issues. A physician or physician designee can administer these assessments on the day of imaging for the florbetapir F 18 imaging session only.

Optional Cerebrospinal fluid (CSF) collection

Depending on site participation, subjects in the Exploratory Phase will be offered to consent for optional CSF collection by LP. A β , phospho-tau, and total tau will be

measured. 20 mL of CSF will be collected from each subject and divided into 1 ml conical vials. Samples will be shipped to a facility designated by the Sponsor. Samples will be identified by the patient number and stored for up to 15 years after the last patient visit for the study at a facility selected by the sponsor

7.3. Protocol for Image Collection

The sponsor will prepare and distribute a PET Imaging Manual for ¹⁸F-AV-1451 and florbetapir F 18. MRI image acquisition parameters and transmission procedures will be outlined in an MRI procedures manual.

7.4. Good Clinical Practice and Monitoring

All clinical studies performed under the direction of Avid/CRO will be conducted in accordance with applicable regulatory requirements and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and Avid/CRO Standard Operating Procedures (SOP).

This includes:

1. IRB/IEC approval: An investigation will be initiated at a study site only after the IRB/IEC 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 legally authorized representative (as appropriate) signs the informed consent form;
3. Recording and monitoring of adverse events as outlined in Section 7.7.3 including the notification of study site clinical investigators, local IRBs and the FDA regarding serious adverse event;
4. Avid RP'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, or their legally authorized representative (as appropriate), will be allowed to read a written informed consent form. The principal investigator or designee will explain all study procedures, risks, and alternative therapies. The subject and legally authorized representative will have an opportunity to have all questions answered by a physician. The subject will then sign and date the informed consent form, indicating willingness to participate in the study.

Subjects 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. When applicable the legally authorized

representative should sign as well, indicating that they have witnessed the subject's consent, and further agree to participate as an informant.

If the subject is not capable of giving consent, consent may be given by a legally 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. If the legal guardian is also the informant, the guardian must still sign the informant line of the form, indicating their own willingness to participate as an informant.

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

7.6. Documentation

¹⁸F-AV-1451 and florbetapir F 18 PET scans, as well as MRI scans, will be saved in an appropriate electronic format as specified in the imaging manuals. A copy of all scans will be saved at the site/imaging center and a copy of each will be forwarded to the sponsor or to the designated imaging core lab as described in the imaging manuals. 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, ECG tracings, etc. All source documentation must be available to Avid and designees. Completed source documents and CRFs may need to be made available and complete for an audit by the FDA or other international regulatory authorities or Avid at any time. A ballpoint pen should be used to ensure that all copies are legible. 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 eCRF. Investigators will be instructed to report to Avid or its designee their assessment of the potential relatedness of each AE to investigational product or protocol procedure via electronic data entry. If a patient's 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 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 eCRF. Signs and symptoms of each AE should be described in detail (e.g., start and stop dates/time, 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 including those that result in a diagnosis should be reported as an AE to Avid or its designee.

7.7.1. Adverse Event Monitoring

Each patient must be carefully monitored for adverse events. This includes clinical laboratory test variables. An assessment must be made of the severity/intensity and relationship to the administration of the trial medication.

7.7.2. Adverse Event Definitions

Adverse Events

For reporting purposes, Avid will distinguish among pre-existing conditions, treatment - emergent adverse events and trial-emergent adverse events. 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 eCRF pages. Signs and symptoms that are believed to be due to the pre-existing condition (started prior to dose of study medication) do not have to be recorded in the AEs section of the eCRF, unless there is an increase in frequency or severity. Additionally, signs or symptoms or changes in pre-existing conditions that occur outside the trial defined adverse event reporting period (e.g., between the end of the baseline/cross-sectional imaging period and the 9 month follow-up imaging period) will be recorded in medical history.

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. For the purposes of this study, untoward medical occurrences will be considered associated with the use of ¹⁸F-AV-1451, and thus be reported as adverse events, if they occur within 48 hours after ¹⁸F-AV-1451 administration, either at baseline or at the 9 or 18 month imaging visit. Untoward medical occurrences will be considered associated with the use of Florbetapir F 18 injection, if they occur within 48 hours after Florbetapir F 18 injection administration. Adverse events associated with the use of ¹⁸F-AV-1451 or Florbetapir F 18 injection will be recorded as treatment emergent relative to the respective drug. Adverse experiences that occur after administration of either drug but outside the 48 hour reporting window will not be reported unless the investigator believes they are attributable to the drug.

In order to capture possible adverse effects of trial participation, trial-emergent adverse events will also be reported as any untoward medical occurrences occurring, during the baseline/cross-sectional imaging period but not during the 48 hour windows following the administration of ¹⁸F-AV-1451 or Florbetapir F 18 injection. For this purpose, the baseline/cross-sectional imaging period will be defined as beginning with the signing of consent and ending 48 hours after the last of the screening/baseline procedures described in sections 7.1.1 – 7.1.3, including (but not limited to) neuropsychological testing, MRI, ¹⁸F-AV-1451 or Florbetapir F 18 injection PET scanning and lumbar puncture.

The end of study for the purpose of adverse event reporting is defined as 48 hours after the last administration (i.e., 18 month visit or early termination visit) of ¹⁸F-AV-1451.

Serious Adverse Event (SAE)

An SAE is an AE 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;
- 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.

Unexpected Adverse Event

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

Relationship to Investigational Product

Investigators will be instructed to report their assessment of the potential relatedness of each adverse event to protocol procedure, concomitant medication and/or investigational product. The assessment of the relationship of an adverse event to the administration of the investigational product is a clinical decision based on all available information at the time of the completion of the eCRF.

Intensity/Severity of an Adverse Event

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

The following classifications should be used:

Mild:

A mild adverse event is an adverse event, usually transient in nature and generally not interfering with normal activities.

Moderate:

A moderate adverse event is an adverse event that is sufficiently discomforting to interfere with normal activities.

Severe:

A severe adverse event is an adverse event 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 adverse events must be fully recorded on the Adverse Event Page via the Electronic Data Capture (EDC) system. Documentation must be supported by an entry in the subject file. Laboratory test, vital signs and ECG abnormalities considered by the Investigator to be clinically relevant should be reported on the Adverse Event page of the eCRF. 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 and laboratory test abnormalities fulfilling the definition of a serious adverse event should, in addition, be reported 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 their 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 receive a dose of investigational product will be collected until 48 hours after the dosing of the investigational product, regardless of the investigator's opinion of causation. Therefore, SAEs that occur later than 48 hours after the dosing of the investigational product are not required to be reported unless the investigator feels the events were related to either investigational product 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 reported 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 statistical analyses will be performed using SAS® version 8.2 or higher.

Data will be summarized using descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, quartiles, minimum, and maximum) for continuous variables and using frequency count and percentage for discrete variables. The demographic and baseline characteristics data will be summarized according to clinical

group (healthy volunteers and subjects with cognitive impairment) at recruitment for all subjects in the safety population. Safety data will be summarized for all patients.

Subject listings of all data from the electronic case report forms (eCRFs) as well as any derived variables will be presented.

Additional details concerning statistical analyses will be included in the Statistical Analysis Plan (SAP).

8.1.1. Sample Size Estimation

8.1.1.1. Exploratory Phase

A total of 230 subjects (80 cognitively healthy volunteers, 80 MCI and 70 AD) will be enrolled in the Exploratory Phase study. To explore the ¹⁸F-AV-1451 SUVR values across age strata among cognitively healthy subjects, these subjects will be divided into 5 age groups as 20-40 years old, 50-59 years old, 60-69 years old, 70-79 years old and 80 years old or above. There will be 15 subjects in each of the 50 or older age groups and about 20 subjects from age group 20-40 years old. From a preliminary analysis of study T807000, the standard deviation (SD) of SUVR from combination ROI was 0.06 for subjects with low probability of AD. Therefore assuming a 0.06 SD, a sample of 15 subjects will give an approximately 90% probability to observe a 95% confidence interval (CI) as accurate as +/-0.04 around the point estimation.

From previous studies, the amyloid positive rate is approximately 50% among MCI patients and approximately 80% from AD subjects. Therefore 80 MCIs and 70 ADs will likely result in 40 amyloid positive MCIs and 56 amyloid positive ADs. Also from study T807000, the combination ROI SUVR difference between CN and AD was 0.39, with a pooled SD of 0.27. Assume a pooled SD of 0.30, a sample of 60 CNs and 56 amyloid positive ADs will give a 90% power to detect a 0.18 difference between the CN and AD groups.

8.1.1.2. Confirmatory Phase

The final hypothesis and endpoint measurements for the Confirmatory Phase are yet to be determined and will depend on the discoveries from Exploratory Phase data. However the primary objective of the confirmatory phase is to validate the accuracy of ¹⁸F-AV-1451 scans to predict clinically significant disease progression within 18 months from scan (e.g., cognitive function deterioration as measured by endpoints based on Exploratory Phase results). For the purpose of sample size calculation, we assumed that the target success criteria would be at least 70% sensitivity and at least 70% specificity for ¹⁸F-AV-1451 scans to detect this deterioration, with the lower bound of 95% confidence intervals (CI) above 50% for both sensitivity and specificity. Preliminary analysis of the exploratory phase cohort data showed that clinical assessments may have a relatively large variance. It is important to ensure that enough subjects will be in each group for sensitivity and specificity calculation (i.e., the subjects with or without a significant disease progression). To that end, we assume at least 20% of the subjects will be in each group at the 18 month follow up. With this assumption, a 5% two-sided type I error rate,

and that 95% CI will be calculated using Wilson score method, a sample of 115 subjects will provide an over 90% probability to observe lower bound of 95% CI above 50%, for both sensitivity and specificity. Also assuming an approximate 20% drop out rate over the 18 months follow up, this study will aim to enroll 150 subjects in total.

8.1.2. Exploratory Phase, Cross-sectional Component

8.1.2.1. Primary Objective Analysis

ANOVA analysis will be applied to detect the difference between clinical diagnosis groups. If an overall difference is detected, pair-wised comparisons will be conducted. If the pre-requisites of ANOVA test are not met, Kruskal Wallis and Wilcoxon rank sum test will be conducted instead.

8.1.2.2. Secondary Objective Analysis

Descriptive statistics will be applied to describe the tau SUVR distribution across age groups among cognitive healthy subjects. These data will also be graphically displayed.

8.1.2.3. Exploratory Objective Analyses

Correlation analysis will be conducted to determine whether greater degrees of cognitive impairment are associated with higher ¹⁸F-AV-1451 uptake in subjects with an amyloid positive status.

Correlation analysis will be conducted to assess the relationship between regional tau deposition measurements with cognitive function measurements and other collected biomarkers.

The association between baseline values in ¹⁸F-AV-1451 uptake in brain and clinical function measures, as well as, biomarkers of neurodegeneration and neurological disease will be explored using the methods described below in **8.1.3.2**.

Subgroup and/or covariate analyses will also be planned accordingly by amyloid beta status, age groups, and etc. The specific analyses to address these objectives will be described in the Statistical Analysis Plan (SAP)

8.1.3. Exploratory Phase, Longitudinal Component

8.1.3.1. Primary Objective Analysis

The primary objective of longitudinal component is to assess the rate of change of tau deposition as measured by ¹⁸F-AV-1451 over time. The tau measurement change from baseline at each follow up visit will be estimated using Mixed Model Repeated Measures (MMRM). The MMRM model will include the following fixed effects: baseline value, clinical group, visit, clinical group by visit interaction, and baseline age. Visit will be considered as a categorical variable. An unstructured covariance matrix will be used to model the within-subject correlation. Least squared means (LSM) and standard error for

the tau value change from baseline will be calculated for each clinical group at every follow up visit.

8.1.3.2. Exploratory objective analyses

The association between change and/or baseline values in ¹⁸F-AV-1451 uptake in brain and clinical function measures, as well as, biomarkers of neurodegeneration and neurological disease (CSF markers including tau, phosphor-tau and beta-amyloid (A β), genetic markers, PET amyloid imaging, brain atrophy assessed by volumetric MRI, and resting connectivity assessed with rsfMRI) will also be assessed using MMRM analyses. Marginal logistic regression and time to event analyses will also applied when appropriate, such as to investigate the odds ratio of ADAS score change over 4 with the tau deposition change over time. The details of these statistical analyses will be provided in SAP.

8.1.4. Confirmatory Phase

Longitudinal data from the exploratory study phase will be assessed periodically to determine the relationships between various ¹⁸F-AV-1451 imaging parameters (e.g., composite and regional SUVR, voxel based statistics and visual interpretation) and the change from baseline in the various cognitive and functional assessments. These data will be used to generate hypotheses regarding the relationship between ¹⁸F-AV-1451 PET tau imaging and cognitive/functional change that will be formally incorporated into an analysis plan and tested in the confirmatory stage of the study.

Based on discoveries using data from Exploratory Phase, a disease progression measurement will be chosen as truth standard (TS), and the accuracy of ¹⁸F-AV-1451 PET scans to detect this TS within 18 months of scan will be evaluated. Hypothesis testing and detailed analyses will be described in a statistical analysis plan (SAP), which will be finalized prior to database lock. Possible analyses include calculation of accuracy measures such as sensitivity, specificity, and two sided 95% confidence intervals (CI) around these rates. Other analyses may include Mixed-Effect Model Repeated Measures (MMRM) analysis, risk ratio analysis, and time to event analysis.

8.2. Safety Analysis

Safety laboratory test results and vital signs measurements will be summarized by subject and by evaluation time point. Change from baseline (pre-dose time point) values will be determined and summarized. Subjects whose laboratory values are outside the pre-determined upper and lower limits of normal will be identified and tabulated.

Adverse events including injection site reactions will be summarized in terms of number and percentage of subjects 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 subjects who experience SAEs or who discontinue due to AEs will be summarized.

Discontinuation

All subjects who discontinued participation prior to completing the study will be listed and their discontinuation reasons will be tabulated.

Laboratory Data

Changes in laboratory data from Baseline will be summarized. Subjects whose laboratory values are outside threshold values will be identified and tabulated.

Vital Signs

Changes in vital signs from baseline will be summarized.

ECG

Mean changes in ECG parameters will be summarized. The average of the two ECG collected prior to administration of ¹⁸F-AV-1451 on imaging day (-10 and -5 min prior to the administration of ¹⁸F-AV-1451), will be used for the baseline estimate. Any subjects showing QTc > 500 or change from baseline of more than 60 msec will be highlighted.

8.3. ¹⁸F-AV-1451 Image Analysis

All ¹⁸F-AV-1451 PET images obtained at baseline and follow-up starting at 80 minutes post injection will be analyzed. ¹⁸F-AV-1451 PET images starting at 110 minutes post injection, for those subjects in which they were acquired, will also be analyzed. The ¹⁸F-AV-1451 PET images will be spatially normalized to standard stereotactic atlas space using MNI brain atlas. The uptake in tau protein rich brain regions will be assessed with regions of interest (ROI, designed in MNI brain atlas) in terms for standard uptake value ratio (SUVr, normalized by cerebellar uptake). The spatially normalized images and the measured SUVr values will be used to accordingly to accomplish the study objectives.

Exploratory analysis will include co-registration of MRI to the ¹⁸F-AV-1451 PET images for ROI creation and/or partial volume correction of ¹⁸F-AV-1451 PET images using anatomical information from MRI data.

Additional analyses may explore various voxel and threshold based approaches.

The final primary method image analysis for the confirmatory phase will be chosen based on results from the exploratory phase before any of the confirmatory phase images are analyzed.

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.

This is a multi-center study. The primary analysis will include data from all centers. A multicenter publication, reporting the primary analysis data set, with authorship from all contributing centers, should precede any other publications.

10. INVESTIGATOR'S REGULATORY OBLIGATIONS

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

10.1. Institutional Review Board (IRB)

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

10.2. Informed Consent

A signed, written informed consent must be obtained from each patient. A copy of the signed informed consent should be given to the patient for their records. A copy of the local IRB/IEC's approved version of the informed consent form must be forwarded to Avid or designee for review prior to being used to obtain patient consent.

10.3. Protocol Adherence

The protocol must be read thoroughly and the instructions must be followed exactly. Where a deviation occurs, 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 Statement of Agreement page;
- Copy of the IRB/IEC and radiation safety committee approval (if applicable);
- Copy of the IRB/IEC stamped approved consent form;
- Name and location of the laboratory utilized for laboratory assays, and other facilities conducting tests, including laboratory certification number and date of certification if available. Avid may be responsible for supplying these to the investigator if a central laboratory is used;
- List of reference range laboratory values. Avid may be responsible for this if a central laboratory is used; and
- Any additional licenses required in order to order to use florbetapir F 18 or ¹⁸F-AV-1451.

10.5. Investigational Product Control

The receipt of clinical supplies (i.e. starting material for ¹⁸F-AV-1451) 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. ¹⁸F-AV-1451 Injection and Florbetapir F18 Injection should be prepared by a qualified PET manufacturing site and administered 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. After completion of the trial, all remaining clinical supplies must be returned to the sponsor or their representative.

10.6. Data Collection

Electronic case report forms (eCRFs) will be used for this trial. Individual patient files should include appropriate source documents, including but not limited to patient's medical records and laboratory test results. The files should include information such as visit dates, records of medical history, examinations administered, laboratory, concomitant treatment, any adverse event encountered and other notes as appropriate. These constitute "source data". All entries on the eCRFs 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/imaging center, and appropriate copies should be forwarded to Avid or a designated Imaging Core Lab as specified in the Imaging Manual.

Each patient'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.

All original laboratory reports must be available for review in each patient's file. It is important that the original reports be available for review because of the possibility of inaccuracies or errors in transcribing data from original records to the eCRF.

The eCRFs 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. The eCRFs must be completed for each patient 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 verify the source data for all information on the eCRF.

10.7. Adverse Events

All adverse events encountered during the clinical trial must be documented on the eCRF, 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 CRF. See section [7.7.4](#) for reporting serious adverse events

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/IEC within 24 hours of receipt.

10.8. Records Retention

All correspondence (e.g., with Avid, IRB/IEC, etc.) relating to this clinical trial should be kept in appropriate file folders. Records of subjects, source documents, and drug inventory sheets pertaining to the trial must be kept on file. Records must be retained until the date a marketing application (NDA) is approved for the drug for the indication for which it is being investigated, or until 3 years following the date of clinical trial termination or completion, whichever is later. If no application is to be filed or if the application is not approved for such indication, records should be kept until 3 years following the date of clinical trial termination or completion.

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.

11. APPENDICES

11.1. References

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11.2. Trial Flow Chart

Exploratory Phase and Confirmatory Phase Cohorts

Evaluations	Screening Visit ^a	Florbetapir F 18 Imaging Visit ^b	End of Florbetapir F 18 Imaging (prior to discharge)	Follow-up Phone Call	¹⁸ F-AV-1451 Imaging Visit ^b	End of ¹⁸ F-AV-1451 Imaging (prior to discharge)	Follow-up Phone Call
Signed Consent	X						
Demographics	X						
Medical History/Neurologic Disease History	X						
Concomitant Meds	X	X			X		
Physical Exam/Neurological Exam	X						
ECG	X				X ^c	X	
Vital Signs	X ^d	X ^e			X ^f	X ^g	
Safety Labs	X				X ^h	X	
Serum beta-hCG ⁱ	X						
Urine Pregnancy test ^j		X			X		
OSU TBI-ID	X						
MMSE	X						
ADAS-Cog 11	X						
Neuropsych battery ^k	X						
MRI of the brain	X						
PET Brain Scan		X			X		
ApoE					X		
Genetic sample					X		
Optional CSF	X ^l						
Evaluation by a physician	X	X ^m	X ^m		X	X	
Adverse Events	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X

- Screening may take place over several days. All assessments must be performed within 30 days of the first ¹⁸F-AV-1451 imaging session (with the exception of the MRI if previously performed).
- The ¹⁸F-AV-1451 and florbetapir F 18 imaging sessions must be performed at least 48 hours apart, but the order of the scans is interchangeable.
- Two ECGs will be taken approximately 5 minutes apart immediately prior to (within approximately 10 minutes) ¹⁸F-AV-1451 Injection administration. One will be taken within 5 minutes after completion of injection.
- Screening vital signs include pulse rate, respiratory rate, supine blood pressure, height and weight
- Vital signs (pulse rate, respiratory rate, supine blood pressure, weight) will be taken immediately prior to injection of florbetapir F 18.
- Pulse, respiratory rate, supine blood pressure, temperature and weight will be taken immediately prior to administration of ¹⁸F-AV-1451. Pulse, respiratory rate, and supine blood pressure within 5 minutes after completion of injection of ¹⁸F-AV-1451 Injection.
- Pulse, respiratory rate, supine blood pressure, temperature
- Blood and urine samples will be collected prior to administration of ¹⁸F-AV-1451 Injection.
- Serum beta-hCG pregnancy test at screening (for females of childbearing potential defined as pre-menopausal or less than 2 years post-menopausal and not surgically sterile).
- For women of childbearing potential, a negative urine pregnancy test must be obtained within 24 hours prior to florbetapir F 18 injection and within 24 hours prior to ¹⁸F-AV-1451 injection.
- Including CDR for subjects in the Confirmatory Cohort.
- CSF collection may occur after the subject has passed screening procedures for subjects in the Exploratory Cohort only
- A physician or physician designee

Longitudinal Component

Exploratory Phase Cohorts ONLY

Evaluations	5 Month Follow-up Phone Call	9 (+/-2) Months First Longitudinal Follow-up Visit	14 Month Follow-up Phone Call	18 (+/-2) Months, Second Longitudinal Follow-up Visit
Updated Medical History	X	X	X	X
Updated Concomitant Meds	X	X	X	X
ECG		X ⁿ		X ⁿ
Vital Signs		X ^o		X ^o
Safety Labs		X ^p		X ^p
Urine Pregnancy test ^q		X		X
MMSE		X		X
ADAS-Cog 11 ^r		X		X
Neuropsych battery, including CDR ^r		X		X
MRI of the brain ^f		X		X
PET Brain Scan		X		X
Follow-up Phone Call ^s		X		X
Evaluation by a physician		X		X
Adverse Events		X		X
Serious Adverse Events		X		X

The First and Second Longitudinal Follow-up Visits will be performed over several days.

- n. Two ECGs will be taken approximately 5 minutes apart immediately prior to (within approximately 10 minutes) ¹⁸F-AV-1451 Injection administration. One will be taken within 5 minutes after completion of injection. One will be obtained at the end of imaging day
- o. Vital signs include pulse rate, respiratory rate, supine blood pressure, temperature and weight
- p. Blood and urine samples will be collected prior to administration of ¹⁸F-AV-1451 Injection and at the end of the imaging day.
- q. For women of childbearing potential, a negative urine pregnancy test must be obtained within 24 hours prior to ¹⁸F-AV-1451 injection.
- r. ADAS-Cog 11, Neuropsych battery, and MRI can be performed +/- 30 days of the ¹⁸F-AV-1451 scan and within 30 days of each other. Assessments should be performed within the specified window of 9 (+/-2) months or 18 (+/-2) months.
- s. Between 2 or 3 business days of the imaging day

Confirmatory Phase Cohort ONLY

Evaluations	5 Month Follow-up Phone Call	9 (+/-) Months, First Longitudinal Follow-up Visit	14 Month Follow-up Phone Call	18 (+/-) Months, Second Longitudinal Follow-up Visit
Updated Medical History	X	X	X	X
Updated Concomitant Meds	X	X	X	X
MMSE		X		X
ADAS-Cog 11		X		X
Neuropsych battery, including CDR		X		X

INVESTIGATOR’S AGREEMENT TO PROTOCOL

Protocol: An open label, multicenter study, evaluating the safety and imaging characteristics of ¹⁸F-AV-1451 in cognitively healthy volunteers, subjects with mild cognitive impairment, and subjects with Alzheimer’s disease

Date and Version: 07 August 2015, Amendment 2

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.

Printed Name

Date

Signature