Protocol Number: ^{18}F-AV-1451-A14

Clinical Evaluation of ^{18}F-AV-1451

Date and Version:

05Sep2014 Amendment 1

Name of Compound:

^{18}F-AV-1451 ([F-18]T807)

Sponsor:

Avid Radiopharmaceuticals

Philadelphia, Pennsylvania USA

Sponsor: Avid Radiopharmaceuticals	**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-A14

"Clinical Evaluation of ^{18}F-AV-1451"

Planned number of subjects (Enrolled):

Approximately 250 subjects including healthy controls and subjects at risk for tau accumulation as defined by the site's companion protocol.

Name of compound: ^{18}F-AV-1451([F-18]T807)

Dose: Up to a target dose 370 MBq (10 mCi)

Route of Administration: Intravenous (IV) bolus

Study Phase: II

Study Centers: Approximately 10 centers in the United States and Canada

Trial Objectives:

The primary objectives of this study are:

- Provide standardized conditions for ^{18}F-AV-1451 use, data collection, and analysis to facilitate evaluation of subject's tau burden.
- To expand the ^{18}F-AV-1451 safety database.

Eligibility:

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

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

1. Male or female subjects at least 18 years of age;
2. Subjects who sign an IRB approved informed consent prior to any study procedures. Where subjects are deemed incapable of informed consent, a legally authorized representative may provide consent, with the subject's documented assent;
3. Subjects who have historical volumetric brain MRI images obtained as part of the site's companion protocol available for submission to Avid; and
4. Subjects who in the opinion of the investigator can tolerate the PET scan procedures.

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals	^{18}F-AV-1451([F-18]T807)	7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole

Subjects will be excluded from enrollment if they:

1. Have clinically significant cardiac, hepatic, renal, pulmonary, metabolic, or endocrine disturbances as indicated by history, which in the opinion of the investigator might pose a potential safety risk to the subject;
2. Have either: 1) Screening ECG with QTc > 450 msec if male or QTc > 470 msec if female; or 2) A history of additional risk factors for Torsades de Pointes (TdP) (e.g., 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); Patients with a prolonged QTc interval in the setting of intraventricular conduction block (examples RBBB or LBBB), may be enrolled with sponsor approval;
3. Have a history of drug or alcohol dependence within the last year, or prior prolonged history of dependence unless approved by the sponsor;
4. 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 or urine β-HCG at the time of screening and negative serum or urine β-HCG on imaging day) 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 ^{18}F-AV-1451 Injection;
5. Have a history of relevant severe drug allergy or hypersensitivity (Relevant severe drug allergies should be determined by the PI, and any questions about a subject's eligibility can be directed to Avid. If a subject has a history of severe drug allergies, it may be dangerous for them to participate in a study);
6. Are patients who have received an investigational medication under an FDA IND protocol within 30 days prior to the planned imaging session for this study, with the exception of medications allowed in the companion study and approval from sponsor. Additionally, the time between the last dose of the previous experimental medication and imaging must be at least equal to 5 times the terminal half-life of the previous experimental medication;
7. Are patients with current clinically significant unstable medical comorbidities, as indicated by history or physical exam that pose a potential safety risk to the subject;
8. Are patients who have received a radiopharmaceutical for imaging or therapy within the past 24 hours prior to the imaging session for this study. If another radiotracer is required in the companion protocol, patients may be able to receive a radiopharmaceutical for imaging or therapy within the 24 hours prior to the imaging session with prior sponsor approval;
9. Are patients who, in the opinion of the investigator, are otherwise unsuitable for a study of this type.

Sponsor:	Name of Compound:	Active Ingredient(s):
Avid Radiopharmaceuticals	^{18}F-AV-1451([F-18]T807)	7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole

Study Design:

Study ^{18}F-AV-1451-A14 is designed to expand the database of ^{18}F-AV-1451 safety and tau binding as measured by PET imaging, and to provide standardized conditions for tau use, data collection and analysis to facilitate companion studies including, but not limited to, longitudinal studies of aging, depression, and traumatic brain injury. Approximately 250 subjects will be studied under this protocol.

Assessments and Endpoints:

Screening:

Screening assessments may take place over several days and will include collection of demographic information, a medical assessment for eligibility, ECG, a brief cognitive assessment (e.g. MMSE), and a traumatic brain injury questionnaire.

^{18}F-AV-1451 PET Imaging Visit:

Subjects who qualify for the study will come to the imaging center at a later date and will have a catheter(s) placed for i.v. administration of ^{18}F-AV-1451. Vital signs will be taken in a supine position immediately prior to administration of ^{18}F-AV-1451 (within 30 minutes prior to injection) and at the completion of imaging prior to subject discharge. Subjects will receive up to a target dose of 370 mBq as a single i.v. bolus of ^{18}F-AV-1451. A 20 minute dynamic image starting approximately 80 minutes post injection will be obtained. With sponsor approval sites may elect an alternative imaging protocol (i.e. different duration or start time) with additional time points. All datasets will be submitted to the sponsor for analysis.

Adverse events will be continuously monitored during the imaging session. Subjects who experience any adverse event will not be discharged until the event has resolved or stabilized.

Repeat Imaging:

Longitudinal imaging studies may be conducted under protocol ^{18}F-AV-1451-A14, with prior sponsor approval. In these studies, subjects may have up to two imaging sessions within a 12 month time-frame. If the second scan is obtained more than 3 months after the previous scan, then the MMSE should be repeated and updates to the OSU-TBI, medical history, and concomitant medications will be collected. Procedures for each imaging day will be identical to those described above.

Follow-Up Phone Call:

A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days after 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.

Details of additional assessments that will be performed at each visit are detailed in Section 7.1.

Sponsor:	**Name of Compound:**	**Active Ingredient(s):**
Avid Radiopharmaceuticals	^{18}F-AV-1451([F-18]T807)	7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole

Statistical Methods:

Descriptive statistics will be applied to describe the distribution of tau deposition as measured by ^{18}F-AV-1451 across clinical diagnosis groups. Safety data will be summarized for patients who received at least one injection of ^{18}F-AV-1451.

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ABBREVIATIONS AND DEFINITIONS

Aβ	Beta amyloid
AD	Alzheimer's disease
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).
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
ECG	Electrocardiogram
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

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
MBq	Megabecquerel
mCi	Millicurie
MHD	Maximum Human Dose
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
NOAEL	No Observable Adverse Effect Level
OSU TBI-ID	Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID)
PET	Positron Emission Tomography
RBT	Repetitive Brain Trauma
SUVR	Standard Uptake Value Ratio
TBI	Traumatic Brain Injury

1. INTRODUCTION

^{18}F-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, Aβ positive, or tau and Aβ 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 i*n vitro* hERG assay, albeit at a concentration more than 40-fold the maximum theoretical AV-1451 plasma concentration. Additionally, *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 species. 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.

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 ^{18}F-labeled compounds such as fluorodeoxyglucose (FDG) and florbetapir F 18 injection.

^{18}F-AV-1451 may be useful as a marker of tau pathology in patients with AD and other neurodegenerative disorders (Figures 1 and 2). Several preliminary studies using ^{18}F-AV-1451 have been completed (e.g., Chien et al., 2013).

The present study is designed to expand the database of ^{18}F-AV-1451 safety and tau binding as measured by PET imaging, and to provide standardized conditions for tau use, data collection, and analysis to facilitate companion studies including, but not limited to, longitudinal studies of aging, depression, and traumatic brain injury.

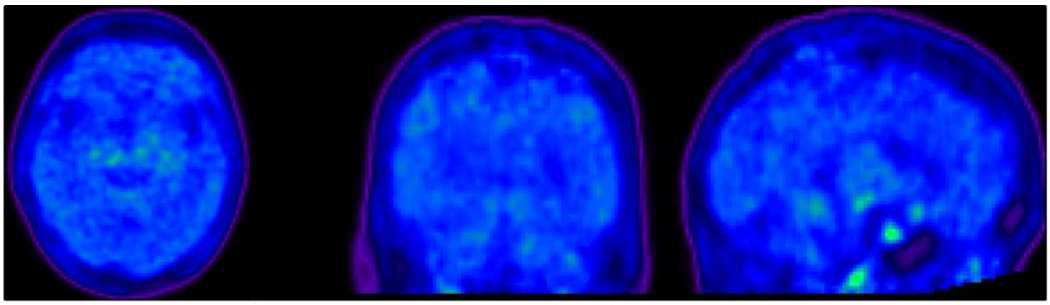


Figure 1: [redacted]**control subject (MMSE = 29)**

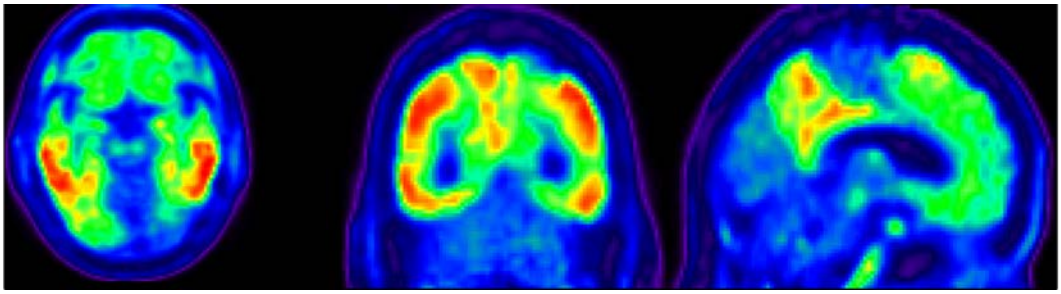


Figure 2: [redacted]**AD subject (MMSE = 18)**

2. TRIAL OBJECTIVES

The primary objectives of this study are:

- Provide standardized conditions for ^{18}F-AV-1451 use, data collection and analysis to facilitate evaluation of subject's tau burden.
- To expand the ^{18}F-AV-1451 safety database.

3. SPONSOR, INVESTIGATOR(S) AND OTHER PARTICIPANTS

The trial is sponsored by:

Avid Radiopharmaceuticals

3711 Market Street, 7th Floor

Philadelphia, PA 19104

Phone: +1 215-298-0700

The medical contact is:

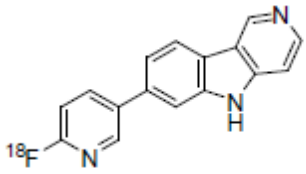
[redacted]

Approximately 10 centers in the United States and Canada will participate.

4. TEST DRUG AND CONTROL AGENTS

4.1. Descriptive Name: ^{18}F AV-1451

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



MW = 262.27 amu

4.2. Radioactive Labeling

The compound is labeled with [^{18}F] 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.

4.3. Decay Characteristics

The time course of radioactive decay for Fluorine [^{18}F] 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 [^{18}F]. Half-life = 109.77 min.

4.4. 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 either:

- 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.

4.5. 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.

4.6. 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

Protocol ^{18}F-AV-1451-A14 is designed to expand the database of ^{18}F-AV-1451 safety and tau binding as measured by PET imaging, and to provide standardized conditions for ^{18}F-AV-1451 use, data collection and analysis to facilitate companion studies looking at tauopathies. Approximately 250 subjects will be studied under this protocol.

Screening assessments may take place over several days and will include the collection of demographic information, a medical assessment for eligibility, ECG, a brief cognitive interview, including an MMSE, and a brain injury questionnaire.

Subjects who qualify for the study will come to the imaging center at a later date and will have catheter(s) placed for i.v. administration of ^{18}F-AV-1451. Vital signs will be taken in a supine position immediately prior to administration of ^{18}F-AV-1451 (within 30 minutes prior to injection) and at the completion of imaging prior to discharge. Subjects will receive a single i.v. bolus of ^{18}F-AV-1451, a 20 minute dynamic scan will be obtained starting approximately 80 minutes post injection. With sponsor approval sites may elect an alternative imaging protocol with additional time points. All datasets will be submitted to the sponsor for analysis.

Adverse events will be continuously monitored during the imaging session. Subjects who experience any adverse event will not be discharged until the event has resolved or stabilized.

A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days after 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 imaging studies may be conducted under protocol ^{18}F-AV-1451-A14, with prior sponsor approval. In these studies subjects may have up to two imaging sessions within a 12 month time-frame. If the second scan is obtained more than 3 months after the previous scan then the MMSE should be repeated and updates to the OSU-TBI, medical history, and concomitant medications will be collected. Procedures for each imaging day will be identical to those described above. Adverse events will not be collected during the time between the first follow-up phone call and the second imaging session, but will be added to the medical history if clinically relevant.

5.1.1. Dosage and Administration

All subjects will receive a single IV bolus administration of up to a target dose of 370 MBq (10 mCi) of ^{18}F-AV-1451 Injection. Where necessary to minimize trial-wise radiation exposure or to comply with local regulations, lower dose may be planned with sponsor approval.

5.1.2. Rationale for Dosages

^{18}F-AV-1451 will be administered IV up to 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 ^{18}F-labeled compounds such as FDG and florbetapir F 18 injection.

The proposed dose has been shown to be well tolerated and to have acceptable image quality in preliminary human studies.

5.2. Selection of Subjects

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

5.2.1. Inclusion Criteria

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

1. Male or female subjects at least 18 years of age;
2. Subjects who sign an IRB approved informed consent prior to any study procedures. Where subjects are deemed incapable of informed consent, a legally authorized representative may provide consent, with the subject's documented assent;
3. Subjects who have historical volumetric brain MRI images obtained as part of the site's companion protocol available for submission to Avid; and
4. Subjects who in the opinion of the investigator can tolerate the PET scan procedures.

5.2.2. Exclusion Criteria

Subjects will be excluded from enrollment if they:

1. Have clinically significant cardiac, hepatic, renal, pulmonary, metabolic, or endocrine disturbances as indicated by history, which in the opinion of the investigator might pose a potential safety risk to the subject;
2. Have either: 1) Screening ECG with QTc > 450 msec if male or QTc > 470 msec if female; or 2) A history of additional risk factors for Torsades de Pointes (TdP) (e.g., 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); Patients with a prolonged QTc interval in the setting of intraventricular conduction block (examples RBBB or LBBB), may be enrolled with sponsor approval;

3. Have a history of drug or alcohol dependence within the last year, or prior prolonged history of dependence unless approved by the sponsor;
4. 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 or urine β-HCG at the time of screening and negative serum or urine β-HCG on imaging day) 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 ^{18}F-AV-1451 Injection;
5. Have a history of relevant severe drug allergy or hypersensitivity (Relevant severe drug allergies should be determined by the PI, and any questions about a subject's eligibility can be directed to Avid. If a subject has a history of severe drug allergies, it may be dangerous for them to participate in a study);
6. Are patients who have received an investigational medication under an FDA IND protocol within 30 days prior to the planned imaging session for this study, with the exception of medications allowed in the companion study and approval from sponsor. Additionally, the time between the last dose of the previous experimental medication and imaging must be at least equal to 5 times the terminal half-life of the previous experimental medication.
7. Are patients with current clinically significant unstable medical comorbidities, as indicated by history or physical exam that pose a potential safety risk to the subject.
8. Are patients who have received a radiopharmaceutical for imaging or therapy within the past 24 hours prior to the imaging session for this study. If another radiotracer is required in the companion protocol, patients may be able to receive a radiopharmaceutical for imaging or therapy within the 24 hours prior to the imaging session with prior sponsor approval;
9. Are patients who, in the opinion of the investigator, are otherwise unsuitable for a study of this type.

5.3. Prior and Concomitant Therapy

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

(other than the study medication), must be documented on the Concomitant Medication Page of the Electronic Case Report Form (eCRF).

- Patients with AD may be on a stable dose of an anticholinesterase and/or Namenda, and may be taking vitamin E at the time of imaging.
- Investigators should carefully consider whether subjects requiring psychotropic medications for behavioral control will be able to complete the imaging session and necessary procedures such as cognitive testing.
- 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).

5.4. 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.
3. Subjects who are being considered for a follow up AV-1451 scan within this protocol must meet all inclusion/exclusion criteria at the time of the second imaging session.

Subjects may be withdrawn from the trial if a SAE occurs. The date and reason for discontinuation should be noted on the eCRF. Subjects who discontinue prematurely should be seen for a final evaluation.

5.5. 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/Contract Research Organization (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 investigator may 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 ^{18}F-AV-1451 Injection can be found in the investigator's brochure.

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

There are no data on the effects of ^{18}F-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 ^{18}F-AV-1451 Injection. ^{18}F-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 Chart)

The study will consist of the following sequence of activities:

7.1.1. Screening:

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

- Informed consent;
- Demographics (age, gender, education, race, ethnicity);
- Medical history, concomitant medications;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of relevant neurologic disease);
- An ECG will be performed to assess the subject's cardiac status. If an ECG was performed within the last 6 months and is available for review, the ECG does not need to be repeated;
- Cognitive status interview, including MMSE and OSU TBI-ID;
- Where appropriate, informant interview with family member or close friend who is familiar with subject's everyday functioning abilities;
- Urine or serum pregnancy test (women of childbearing potential);
- A physician will see the patient during the screening visit.

Demographic information, cognitive status assessment, MMSE, and OSU TBI-ID collected within the last 60 days as part of a companion protocol or clinic visit need not be repeated.

7.1.2. Imaging Visit

^{18}F-AV-1451 PET Imaging Visit

The following assessments will be performed for all subjects:

- Females of childbearing potential will have a urine or serum pregnancy test prior to injection (the result must be negative for the subject to be administered ^{18}F-AV-1451);
- Vital signs will be taken in a supine position immediately prior to administration of ^{18}F-AV-1451 (within 30 minutes prior to injection) and at the completion of imaging at discharge.
- Body weight and height will be measured prior to injection.
- ^{18}F-AV-1451 will be administered, a 20 minute dynamic image will begin approximately 80 minutes post-injection. The images will be reconstructed immediately after the scan. With sponsor approval, sites may elect an alternative imaging protocol with additional time points. All datasets will be submitted to the sponsor for analysis.
- Subjects will be observed continuously for signs of adverse events, or serious adverse events;
- A physician will see the patient prior to dosing and prior to discharge.

7.1.3. Follow-Up:

A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days after 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.

7.1.4. Repeat Imaging:

Longitudinal imaging studies may be conducted under protocol ^{18}F-AV-1451-A14, with prior sponsor approval. In these studies subjects may have up to two imaging sessions within a 12 month timeframe. If the second scan is obtained more than 3 months after the previous scan then the MMSE should be repeated and updates to the medical history, OSU-TBI and concomitant medications will be collected. Procedures for each imaging day will be identical to those described above.

7.2. Observations and Measurements

Informed Consent

Potential subjects 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

their willingness to participate in the study (see Section 7.5). A copy of the signed informed consent will be given to the subject.

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

Medical History

The investigator, or designee, will obtain an updated history at the screening visit.

- Relevant demographic information
- Review of body systems
- Social history
- Medical and surgical history, including medical care for head trauma
- Concurrent medications

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

Electrocardiogram

A resting ECG will be recorded at screening if a previous ECG performed within the last 6 months is not available for review.

MRI

Electronic copies of historical volumetric brain MRI scans obtained as part of the site's companion protocol will be submitted to Avid, or designated imaging core lab.

Vital Signs

Vital signs (pulse rate, respiratory rate, blood pressure) will be taken as part of the imaging day procedures in the supine position prior to injection and at the completion of imaging at discharge.

Height and Weight

At the imaging visit (prior to ^{18}F-AV-1451 dose administration) body weight and height will be measured, lightly clothed.

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.

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

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.

Physician Visit

A physician must see the subject at screening, prior to drug administration and at study end, prior to discharge from the ^{18}F-AV-1451 imaging session. At discharge, the physician should review all safety data and briefly examine/query the subject regarding potential adverse events, or other treatment issues.

Pregnancy Testing

Serum beta hCG or Urine beta hCG: performed at screening and imaging day prior to injection for females of childbearing potential (defined as pre-menopausal or less than 2 years post-menopausal or not surgically sterile).

7.3. Protocol for Image Collection

The sponsor will prepare and distribute imaging manuals for ^{18}F-AV-1451 image acquisition parameters and transmission procedures prior to site initiation.

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 approval: An investigation will be initiated at a study site only after the IRB for that study site has given their written approval of the protocol and informed consent;
2. Informed Consent: Study procedures will not be initiated until the subject 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.

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 for their records.

7.6. Documentation

^{18}F-AV-1451 scans will be saved in an appropriate electronic format as specified in the imaging manuals. All other data required by the protocol will be recorded in the eCRFs. All data in the eCRFs 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 eCRFs may need to be made available and complete for an audit by the FDA, other international regulatory authorities, or Avid at any time. eCRFs 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 eCRFs. Investigators will be instructed to report to Avid or its designee their assessment of the potential relatedness of each AE to study drug 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 eCRFs. Signs and symptoms of each AE should be described in detail (e.g., start and stop dates/time, severity/intensity, relationship to study drug, 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 study drug.

7.7.2. Adverse Event Definitions

Adverse Events

An adverse event is any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the study drug.

For reporting purposes, Avid will distinguish among pre-existing conditions, trial-emergent adverse events and treatment-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 eCRF pages. During the study, site personnel will record any change in the condition(s) and occurrence and nature of any AEs. Signs and symptoms that are believed to be due to the pre-existing condition under study (started prior to dose of study medication) do not have to be recorded in the AEs section of the eCRF, unless there is an increasing in frequency and severity.

Trial-emergent adverse events are undesirable experiences, signs or symptoms that begin, or worsen in intensity or frequency, after the informed consent, and prior to administration of study drug (^{18}F-AV-1451) at the imaging visit. These will be recorded on the adverse event eCRFs.

Treatment-emergent adverse events are undesirable experiences, signs, or symptoms associated with the use of a study drugs. For the purposes of this study an adverse event will be considered associated with the use of ^{18}F-AV-1451 if it begins or worsens in intensity or frequency within 48 hours after the administration of ^{18}F-AV-1451. Adverse experiences that occur after administration of study drug but outside the 48 hour reporting window will not be reported unless the investigator believes they are attributable to the drug.

The end of study for the purpose of adverse event reporting is defined as 48 hours after the administration of ^{18}F-AV-1451 Injection.

Serious Adverse Event (SAE)

A 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 a 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 Study Drug

Investigators will be instructed to report their assessment of the potential relatedness of each adverse event to protocol procedure or study drug. The assessment of the relationship of an adverse event to the administration of the study drug 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 study drug 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 eCRFs. Documentation must be supported by an entry in the subject file. Laboratory tests, vital signs and ECG abnormalities considered by the Investigator to be clinically relevant should be reported on the adverse event eCRFs. Signs and symptoms of each AE should be described in detail (e.g., start and stop dates, severity/intensity, relationship to study drug, 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 study drug will be collected until 48 hours after the dosing of the study drug, regardless of the investigator's opinion of causation. Therefore, SAEs that occur later than 48 hours after the dosing of the study drug are not required to be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

If a patient experiences a SAE after signing informed consent, but prior to receiving study drug, 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.

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

Frequency distributions including counts and percentages will be included for all categorical outcome variables. All continuous outcome variables will be summarized with statistics including mean, standard deviation, median, minimum and maximum values.

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

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

8.1.1. Populations for Analysis

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

population will include all patients that received at least one dose of ^{18}F-AV-1451 compound. Safety evaluation will be based on safety population.

8.2. Analyses

8.2.1. Efficacy Analyses

^{18}F-AV-1451 images will be evaluated to determine if the tracer shows favorable characteristics for further development as a tau protein imaging agent. Descriptive statistics will be applied to describe the distribution of tau deposition as measured by ^{18}F-AV-1451 across clinical diagnosis groups. Mean, standard deviation, median, minimum, and maximum values will be provided for continuous variables and counts and percentages will be provided for categorical variables

8.2.2. Safety Analyses

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

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. A multi-center publication, reporting the primary analysis data set, 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 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 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 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'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 and radiation safety committee approval (if applicable);
- Copy of the IRB 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 ^{18}F-AV-1451.

10.5. Study Drug Control

The receipt of clinical supplies 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. ^{18}F-AV-1451 Injection should be prepared by a qualified PET manufacturing site and administered by a qualified individual under the investigator's supervision. 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 eCRF. See section 7.7.4 for reporting serious adverse events.

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

10.8. Records Retention

All correspondence (e.g., with Avid, IRB, etc.) relating to this clinical trial should be kept in appropriate file folders. Records of subjects, source documents, 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 2 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 2 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

Albert, M. S., DeKosky, S. T., Dickson, D., et al. “The diagnosis of mild cognitive impairment due to Alzheimer’s disease: Recommendations from the National Institute on Aging and Alzheimer’s Association workgroup.” The Alzheimer’s Association. Alzheimer’s and Dementia, 1-10, 2011.

Chien, D.T., Bahri, S., Szardenings, A.K., Walsh, J.C., Mu, F., Su, M.Y., Shankle, W.R., Elizarov, A., Kolb, H.C., “Early clinical PET imaging results with the novel PHF-tau radioligand [18F]-T807.” J Alzheimers Dis, 2013 Jan 1l34(2):467-68.

Corrigan, J.D., & Bogner, J. (2007). Initial reliability and validity of the Ohio State University TBI identification method. Journal of Head Trauma Rehabilitation, 22, 318 – 329.

Folstein, M.R., Folstein, S.E., and McHugh, P.R. “Mini Mental State: A practical method for grading the cognitive status of patients for the clinician.” Journal of Psychiatric Research, 12: 189-198, 1975.

McKhann, G.M., Knopman, D.S., Chertkow, H., et al. “The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease”. Alzheimers Dement. May 2011;7(3):263-269.

Xia, C.F., et al. “[18F]T807, a novel tau positron emission tomography imaging agent for Alzheimer’s disease,” Alzheimers Dement. 2013, 1-11.

11.2. Trial Flow Chart

Evaluations	Screen	Pre-dose	Dose	PET Imaging	End of Imaging	2 – 3 days post injection
Signed Consent	X					
Medical / Disease History	X					
Concomitant Meds	X	X				
ECG	X					
MMSE	X					
Physician Visit	X	X			X	
OSU TBI-ID	X					
Vital Signs[2]		X			X	
Pregnancy Test	X	X				
^{18}F-AV-1451 Administration			X			
PET Imaging[1]				Continuous 20 minute scan		
Follow-up Phone Call						X
Adverse Event Assessment	X	X	X	X	X	X

[1]Sites may elect to perform additional imaging time points with prior sponsor approval.

[2]Height and weight will be measured prior to injection on imaging day.

11.3. Guidelines for diagnostic classification

Subjects meeting the NINCDS-ADRDA criteria (McKhann 2011) should be classified as **possible or probable AD**:

1. Patients with dementia as evidenced by a MMSE score typically ranging from 10 to 24, boundaries included, at screening;
2. Patients whose history of cognitive decline has been gradual in onset and progressive over months to years. Evidence should be present indicating sustained memory deterioration in an otherwise cognitively normal patient, plus additional cognitive deficits in another cognitive function such as: learning, language presentation, visuospatial presentation, and executive dysfunction.

Subjects who meet the following NIA-Alzheimer's Association working group's diagnostic guidelines for AD: Alzheimer's Dementia 7:270-9, 2011 (Albert 2011), criteria should be classified as **mild cognitive impairment:**

1. Have cognitive decline verified by the study physician.
2. Evidence of objective impairment in one or more cognitive domains, with supporting evidence from objective testing if available.
3. Preservation of independence in functional abilities.
4. Not demented.
5. Patients typically with an MMSE score $\geq$ 24.

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

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

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

INVESTIGATOR'S AGREEMENT TO PROTOCOL

Protocol ^{18}F-AV-1451-A14: "Clinical Evaluation of ^{18}F-AV-1451"

Date and Version: 05Sep2014 Amendment 1

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