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Study Protocol: 18F-AV-1451-A13

Official Title: A High Resolution Autopsy Study Evaluating the Relationship of 18F-AV-1451 PET Imaging and Tau Pathology

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A High Resolution Autopsy Study Evaluating the Relationship of ^{18}F-AV-1451 PET Imaging and Tau Pathology

Date and Version:

14Nov2016 - Amendment 3

Name of Compound:

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

Sponsor:

Avid Radiopharmaceuticals, Inc.

Philadelphia, Pennsylvania USA

Approval/Signature:

PPD

PPD

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

Title of Study:

^{18}F-AV-1451-A13: A High Resolution Autopsy Study Evaluating the Relationship of ^{18}F-AV-1451 PET Imaging and Tau Pathology

Test Product: ^{18}F-AV-1451

Dose: 370 MBq (10mCi)

Route of Administration: Intravenous (IV) bolus

Study Phase: I

Study Centers: 1 – 4 centers in the United States

Trial Objectives:

To explore the relationship between ^{18}F-AV-1451 PET scan results and brain pathology observed at autopsy.

Planned number of subjects to be enrolled:

Up to 10 subjects will be enrolled and imaged with ^{18}F-AV-1451. All subjects will be followed to autopsy. A subset of approximately 5 brains will be selected for high resolution analysis.

Eligibility:

Subjects may be enrolled if they:

1. Are males or females between 60 and 89 years of age;
2. Have a projected life expectancy of ≤ 6 months as determined by the site principal investigator;
3. Can tolerate an MRI and 20 minute PET scan. The site principal investigator will carefully assess each patient and use sound medical judgment to determine whether the patient can tolerate both scan procedures; and
4. Give informed consent or have a legally authorized representative (LAR) to consent for study procedures and brain donation consistent with the legal requirements of the state where the study is conducted.

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

Subjects may not be enrolled if they:

1. Have primary brain tumor, known metastases to the brain, central nervous system (CNS) lymphoma;
2. Have any major, focal structural brain lesion that would interfere with interpretation of PET images;
3. Are aggressively being treated with life sustaining measures (e.g. currently on respirator; receiving high dose chemotherapy – subjects on low maintenance dose or between dose cycles may be enrolled after consultation with Avid);
4. Have a clinically significant infectious disease, including Human Immunodeficiency Virus (HIV) infection, hepatitis or prion disease;
5. Are receiving any investigational medications, or have participated in a trial with investigational medications within the last 30 days;
6. Are females of childbearing potential who are pregnant or are not using adequate contraception;
7. A history of additional risk factors for Torsades de Pointes (TdP) or are taking drugs that are known to cause QT-prolongation (a list of prohibited and discouraged medications is provided by the Sponsor).

Study Design:

The study is designed to examine the relationship between imaging results detected on a ^{18}F-AV-1451 PET scan and pathology found at autopsy within six months of imaging. The participating clinical centers will make an effort to enroll subjects with various levels of cognitive status, ranging from cognitively normal through dementia.

Screening assessments may take place over several days and will include collection of demographic information, diagnostic interview, brain MRI, and safety assessments. At the time of screening, subjects and/or next-of-kin will be asked to provide consent for brain donation in addition to providing informed consent for the screening and imaging procedures in the study.

Subjects who qualify for the study will receive a single I.V. bolus of ^{18}F-AV-1451 followed by brain PET imaging for 20 minutes duration, beginning approximately 80 minutes post-injection. Vital signs will be obtained prior to the administration of ^{18}F-AV-1451 and at the completion of the imaging session. Adverse events will be continuously monitored during the imaging session. Subjects who experience an adverse event will not be released until the event has been resolved or stabilized. After the 48 hour safety follow-up is completed subject participation in the study will end.

Sponsor:	**Name of Compound:**	**Active Ingredient(s):**
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Study Analysis:
An exploratory analysis will be performed to compare the relationship of ^{18}F-AV-1451 PET scan results and tau accumulation at autopsy within six months of imaging on a regional and global basis.

The ^{18}F-AV-1451 PET imaging results of the 10 subjects will be analyzed on a subject by subject basis. The tau levels seen on the ^{18}F-AV-1451 PET scan will determine which subjects will get high resolution brain analysis at autopsy to ensure recruited subjects have a full range of tau distribution.

Assessments and Endpoints:

Screening may take place over several days. Some screening assessments may be performed on imaging day. Assessments will include:

- Informed consent (for clinical, imaging and autopsy procedures);
- Demographics (age, gender, race, ethnicity, education);
- Brief cognitive / dementia evaluation including:
  - Medical history and concomitant medications;
  - Alzheimer's disease history (if relevant: date/months since symptom onset, date/months since diagnosis, family history of neurological disease);
  - Mini-Mental Status Examination (MMSE) may be obtained if the subject is able to cooperate with the test;
  - IQCODE will be administered to the subject's caregiver/informant to include information about clinically meaningful decline in cognitive status during the ten years prior to the subject's most recent illness;
    Note: If an informant is not available to provide information for the IQCODE this will not necessarily result in exclusion for the subject.
- Safety (vital signs);
- Most recent height and weight will be obtained from medical records;
- Urine pregnancy test (for females of childbearing potential);
- Brain MRI (MRI should be performed within 2 weeks of the ^{18}F-AV-1451 PET scan); and
- A physician evaluation and summary of current medical status.

^{18}F-AV-1451 Imaging Day:

The following assessments will be performed for all subjects on the imaging day:
- Any procedure not completed during the screening visit;
- The subject will be seen by a physician who will assess their ability to safely tolerate the imaging procedure;

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

- Females of childbearing potential will have a urine (or serum if required by local IRB) pregnancy test prior to injection (the result must be negative for the subject to be administered ^{18}F-AV-1451);
- Following an I.V. bolus injection of ^{18}F-AV-1451, 20 minutes of continuous brain PET imaging will begin 80 minutes post-injection;
- Vital signs will be taken immediately prior to administration of ^{18}F-AV-1451 and after completion of imaging, prior to discharge;
- Subjects will be observed continuously for signs of adverse events (AE) or serious adverse events (SAE). All AEs and SAEs will be followed until resolution or stabilization;
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected; and
- A physician will see the subject prior to release from the PET center to evaluate any adverse events.

Safety Follow-up/Phone Call:

Each study subject (or caregiver/informant if applicable) will be contacted 2 or 3 business days after ^{18}F-AV-1451 administration, but not prior to 48 hours post-injection, to collect any new adverse events. End of study for the purpose of adverse event reporting and study participation is defined as 48 hours after ^{18}F-AV-1451 administration.

Evaluation of Imaging:

^{18}F-AV-1451 PET images will have quantitative and qualitative analysis performed for regional and global distribution.

Neuropathology Evaluation:

All neuropathology methods and analysis will be detailed in a separate neuropathology manual, which will be written prior to the first subject autopsy in this study.

Statistical Methods: Descriptive statistics will be applied to summarize the autopsy findings and tau deposition as measured by ^{18}F-AV-1451 uptake. A correlation analysis will be applied to explore the relationship of tau at ^{18}F-AV-1451 PET scan and at autopsy on a regional and global basis.

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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.
AIDS	Acquired Immune Deficiency Syndrome
amu	Atomic mass unit
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).
CFR	Code of Federal Regulations
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
EDC	Electronic Data Capture
Efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.
FDA	US Food and Drug Administration
FDG	[18]F – Fluorodeoxyglucose
FTD	frontotemporal dementia

GCP	Good Clinical Practice
hERG	human Ether-à-go-go-Related Gene is a gene that codes for a protein known as Kv11.1, the alpha subunit of a potassium ion channel.
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH/IEC	International Conference on Harmonization/Independent Ethics Committee
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IRB	Institutional Review Board
Kd	a specific type of equilibrium constant that measures the propensity of a larger object to separate (dissociate) reversibly into smaller components, as when a complex falls apart into its component molecules, or when a salt splits up into its component ions.
keV	kiloelectron volt
ICH	International Conference on Harmonization
IND	Investigational New Drug
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
MedDRA	Medical Dictionary for Regulatory Activities
MHD	Maximum Human Dose
µg	microgram
mM	millimeter
MMSE	Mini Mental State Examination

MRI	Magnetic Resonance Imaging
mSv	The Sievert is a derived unit of ionizing radiation dose in the International System of Units (SI)
MW	Molecular Weight
N	Number of subjects
NDA	New Drug Application
nM	nanometer
NOAEL	No Observable Adverse Effect Level
PET	Positron emission tomography
PHF	Paired helical filament is a major component of the neurofibrillary tangles involved in the pathology of Alzheimer's disease
PhRMA	Pharmaceutical Research and Manufacturers of America
SAP	Statistics Analysis Plan
SD	Standard deviation
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.
SOC	System Organ Class
SUVR	Standard Uptake Value Ratio
TBI	Traumatic Brain Injury
TDP	Torsades de Pointes
USP	Ultraspiracle protein, a part of the ecdysone receptor
v/v	Volume concentration

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 (Aβ) neuritic plaque deposition, a hallmark pathology, and a required element for the evaluation of AD neuropathologic change (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 shown to predict rate of future deterioration and has not been established as a tool to predict or monitor response to therapy.

Deposited tau is one of the defining neuropathological lesions of AD, but is also one of the hallmark pathologic features of other dementias, including frontotemporal dementia (FTD) [Bigio 2008; Cairns 2007; Piguet 2011]. In contrast to Aβ neuritic plaques, the density and distribution of phosphorylated tau, aggregated in neurofibrillary tangles, increases with AD related cognitive impairment and correlates with neurodegeneration (Duyckaerts et al., 1987; Braak et al., 2011; Nelson et al., 2012). Thus a PET imaging agent that binds to phosphorylated tau has potential application as biomarker for disease severity/neurodegeneration and may be useful both for selecting patients for therapy and for monitoring disease progression in therapeutic trials.

[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 Kd of 15nM. A saturation binding experiment using purified PHF tau isolated brains of AD patients yielded a Kd 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.

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.

Preliminary analyses of human ^{18}F-AV-1451 PET images from human subjects have shown little accumulation of tracer in young subject, accumulation largely limited to medial temporal lobe in older subjects with clinically normal cognition, and increased accumulation in cortical areas of amyloid positive MCI and AD subjects. Although these preliminary results are consistent with the pattern of tau pathology previously reported in autopsy studies (Braak, 1991) and suggest ^{18}F-AV-1451 may be useful as a marker of tau pathology in patients with AD and other neurodegenerative disorders, additional studies are needed to confirm that the *in vivo* ^{18}F-AV-1451 PET signal specifically reflects brain tau accumulation. Thus, the present study is intended to explore the relationship between ^{18}F-AV-1451 PET scan signal and brain tau pathology as seen at autopsy.

2. TRIAL OBJECTIVES

To explore the relationship between ^{18}F-AV-1451 PET scan results and brain pathology observed at autopsy.

3. SPONSOR, INVESTIGATOR(S) AND OTHER PARTICIPANTS

The trial is sponsored by:

Avid Radiopharmaceuticals, Inc.
3711 Market Street, 7th Floor
Philadelphia, PA 19104
Phone: +1 215-298-0700

The medical contact is:

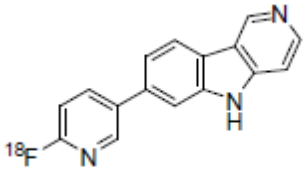
PPD M.D.
PPD
Office: PPD
Fax: PPD
E-mail: PPD

This study will be conducted at 1 to 4 centers in the United States.

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

The study is designed to examine the relationship between imaging results detected on a ^{18}F-AV-1451 PET scan and pathology found at autopsy within six months of imaging. Up to 10 subjects will be enrolled and imaged with ^{18}F-AV-1451. All subjects will be followed to autopsy. Approximately 5 brains will be selected for high resolution analysis.

All subjects and/or their LAR/next-of-kin will provide informed consent before starting any study procedures.

Screening assessments may take place over several days and will include collection of demographic information, diagnostic interview, brain MRI, and safety assessments. At the time of screening, subjects and/or their LAR/next-of-kin will be asked to provide consent for brain donation in addition to providing informed consent for the screening and imaging procedures in the study.

Subjects who qualify for the study will receive a single I.V. bolus of ^{18}F-AV-1451 followed by brain PET imaging for 20 minutes duration, beginning approximately 80 minutes post-injection. Vital signs will be obtained prior to the administration of ^{18}F-AV-1451 and at the completion of the imaging session. Adverse events will be continuously monitored during the imaging session. Subjects who experience an adverse event will not be released from the PET center until the event has been resolved or stabilized. After the 48 hour safety visit or follow-up phone call is completed subject participation in the study will end.

5.2. Planned Dosage and Duration of Treatment

5.2.1. Dosage and Administration

^{18}F-AV-1451:

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

5.2.2. Rationale for Dosages

^{18}F-AV-1451 will be administered IV in a radioactive dose of 370 MBq with a maximum human 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 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 the following criteria are eligible to enroll in this trial:

1. Are males or females between 60 and 89 years of age;
2. Have a projected life expectancy of ≤ 6 months as determined by the site principal investigator;
3. Can tolerate an MRI and 20 minute PET scan. The site principal investigator will carefully assess each patient and use sound medical judgment to determine whether the patient can tolerate both scan procedures; and
4. Give informed consent or have a legally authorized representative to consent for study procedures and brain donation consistent with the legal requirements of the state where the study is conducted.

5.3.2. Exclusion Criteria

Subjects may not be enrolled if they:

1. Have primary brain tumor, known metastases to the brain, central nervous system (CNS) lymphoma;
2. Have any major, focal structural brain lesion that would interfere with interpretation of PET images;
3. Are aggressively being treated with life sustaining measures (e.g. currently on respirator; receiving high dose chemotherapy – subjects on low maintenance dose or between dose cycles may be enrolled after consultation with Avid);
4. Have a clinically significant infectious disease, including Human Immunodeficiency Virus (HIV) infection, hepatitis or prion disease;
5. Are receiving any investigational medications, or have participated in a trial with investigational medications within the last 30 days;
6. Are females of childbearing potential who are pregnant or are not using adequate contraception;
7. A history of additional risk factors for Torsades de Pointes (TdP) or are taking drugs that are known to cause QT-prolongation (a list of prohibited and discouraged medications is provided by the Sponsor).

5.4. Prior and Concomitant Therapy

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 on the Concomitant Medication Page of the eCRF.

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).

5.5. 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 eCRF.

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 ^{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 relatively little toxicological evaluation has been completed, and 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. 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.

7.1.1. Screening Visit

Screening may take place over several days. Some screening assessments may be performed on imaging day.

Assessments will include:

- Informed consent (for clinical, imaging and autopsy procedures);
- Demographics (age, gender, race, ethnicity, education);
- Brief cognitive / dementia evaluation including:
  - Medical history and concomitant medications;
  - Alzheimer's disease history (if relevant: date/months since symptom onset, date/months since diagnosis, family history of neurological disease);
  - Mini-Mental Status Examination (MMSE) may be obtained if the subject is able to cooperate with the test;
  - IQCODE will be administered to the subject's caregiver/informant to include information about clinically meaningful decline in cognitive status during the ten years prior to the subject's most recent illness;; **Note:** If an informant is not available to provide information for the IQCODE this will not necessarily result in exclusion for the subject.
- Safety (vital signs);
- Most recent height and weight will be obtained from medical records;
- Urine pregnancy test (for females of childbearing potential);
- Brain MRI (MRI should be performed within 2 weeks of the [18]F-AV-1451 PET scan);
- A physician evaluation and summary of current medical status.

7.1.2. [18]F-AV-1451 PET Imaging Day

The following assessments will be performed for subjects on imaging day:

- Any procedure not completed during the screening visit;
- The subject will be seen by a physician who will assess their ability to safely tolerate the imaging procedure;
- Females of childbearing potential will have a urine (or serum if required by local IRB) pregnancy test prior to injection (the result must be negative for the subject to be administered [18]F-AV-1451);
- Following an I.V. bolus injection of [18]F-AV-1451, 20 minutes of continuous brain PET imaging will begin 80 minutes post-injection;
- Vital signs will be taken immediately prior to administration of [18]F-AV-1451 and after completion of imaging, prior to discharge;
- Subjects will be observed continuously for signs of adverse events (AE) or serious adverse events (SAE). All AEs and SAEs will be followed until resolution or stabilization;
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected; and
- A physician will see the subject prior to release from the PET center to evaluate any adverse events.

7.1.3. Safety Follow-up/Phone Call:

Each study subject (or caregiver/informant if applicable) will be contacted 2 or 3 business days after ^{18}F-AV-1451 administration, but not prior to 48 hours post-injection, to collect any new adverse events. End of study for the purpose of adverse event reporting and study participation is defined as 48 hours after ^{18}F-AV-1451 administration.

7.2. Observations and Measurements

Autopsy:

For those subjects who come to autopsy within six months of imaging, neuropathological examination will be conducted according to a separate neuropathology manual, which will be written prior to the first subject autopsy in this study. Cases not included in the high-resolution autopsy study will be banked until the time of study conclusion. At this time, a clinical autopsy may be conducted and a clinical autopsy report provided to the subject's physician.

Brain tissue will be maintained at the Grinberg Lab/UCSF until 2 years after the study is completed for study purposes. After that period of time, brain tissue will be placed in a biospecimen repository located at the Grinsberg Lab/UCSF for future research studies. Approved research studies may be conducted at the VA, other Federal health agencies, academic institutions, or for-profit organizations. Brain tissue will only be provided to researchers in a coded manner so that they will not be able to identify participants. If participant does not consent to allow his/her brain tissue to be placed into this biospecimen repository, he/she cannot participate in this study.

Informed Consent

Potential subjects and legally authorized representatives, if applicable, will be allowed to read a written informed consent form. The site 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.

IQCODE – Short Version (Jorm, 1994)

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) is a tool used to assess cognitive impairment in older people. IQCODE will be administered to subject's caregiver/informant during screening.

Medical History, Neurologic Disease History

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

- Relevant demographic information
- Medical and surgical history

- Concurrent medications
- Alzheimer's 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.

Documentation of the events leading up to death will be collected.

MRI

The screening brain MRI should be obtained within 2 weeks of the ^{18}F-AV-1451 PET scan. A second brain MRI will be taken post-mortem to help correct for brain deformations when co-registering histology and PET scan data. The post-mortem MRI can be done in vivo or in a 3D printed skull. The MRI sequences and acquisition parameters will be described in a separate document. Electronic copies of MRI scans will be submitted to Avid.

Pregnancy Testing

A urine beta-hCG test will be performed at screening and at the ^{18}F-AV-1451 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). A serum pregnancy test may also be obtained prior to injection at the ^{18}F-AV-1451 imaging visit(s) if required by the local site.

Vital Signs

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

- Screening Visit;
- Immediately prior to the administration of ^{18}F-AV-1451 Injection;
- After the completion of imaging prior to discharge;

The most recent height and weight recorded in the subject's medical records will be collected at screening.

7.3. Protocol for Image Collection

The sponsor will prepare and distribute a PET Imaging Manual for ^{18}F-AV-1451 as well as an MRI 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 including the notification of study site clinical investigators, local IRBs and the FDA regarding serious adverse events;
4. Avid's obligation to monitor the participating center on a regular basis; and
5. The termination of a center or the trial if conditions apply, as outlined in Section 5.6.

7.5. Informed Consent and Subject Information

Potential subjects, or their legally authorized representative (as appropriate), will be allowed to read a written informed consent form. The site 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.

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

^{18}F-AV-1451 PET scans and 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 eCRF. All data in the eCRF 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 or other international regulatory authorities or Avid at any time. A ballpoint pen should be used to ensure that all copies are legible. eCRFs and all other records must be filed in accordance with applicable laws and regulations (see Section 10.6)

7.7. Adverse Events

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 Even 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.

In order to capture possible adverse effects of trial participation, any untoward medical occurrences occurring after the informed consent until the administration of [18]F-AV-1451 will be recorded in the CRF for reporting as trial-emergent adverse events.

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Untoward medical occurrences will be considered associated with the use of [18]F-AV-1451, and thus be reported as adverse events, if

they occur within 48 hours after ^{18}F-AV-1451 administration. Adverse experiences that occur after administration of ^{18}F-AV-1451 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 last administration of ^{18}F-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.

In the context of this study, death occurring after the 48 hour safety follow-up is expected and will not be considered a reportable SAE in the clinical or Global Patient Safety databases unless the investigator believes the death is caused by the investigational product or protocol procedure.

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 eCRFs. Documentation must be supported by an entry in the subject file. Vital signs 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 receives 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 in the clinical or Global Patient Safety databases 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 be reported on the eCRF and to Eli Lilly or its designee. 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 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).

8.2. Safety Analysis

Vital signs measurements will be summarized by subject. Change from baseline (pre-dose time point) values will be determined and summarized.

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.

8.3. Image Analysis

All ^{18}F-AV-1451 PET images will be analyzed and include co-registration of the MRI to the PET images. The exploratory analysis will be detailed in the Image Analysis Plan.

8.4. Primary Objective Analysis

The relationship of tau at ^{18}F-AV-1451 PET scan and at autopsy will be graphically displayed on a regional and global basis. Pearson product correlation analysis will be applied to quantify this relationship, if there are no obvious outliers. If there are obvious outliers, a Spearman's rank correlation analysis will be applied instead.

8.5. Sample Size

Due to the exploration nature of this study, the sample size was determined outside of statistical considerations.

9. USE OF DATA AND PUBLICATION

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

- We commit to timely communication of meaningful results of controlled clinical trials, regardless of outcome.

- As a sponsor, we may recommend that the Investigator(s) delay or decline publication in cases where the study design, conduct, or data are insufficient to allow meaningful interpretation. Avid and the Investigator(s) will discuss the study design and data in advance of the study, and again after completion, and will strive, through appropriate scientific debate, to reach a consensus regarding the potential merits of publication.
- Avid retains the right to review any manuscripts, presentations, or abstracts before they are submitted for publication. Where differences of opinion or interpretation exist regarding data planned for publication, the parties (Avid and the Investigator) should try to resolve them through appropriate scientific debate. Avid retains the right to delay publication for up to 60 days to protect intellectual property.
- Anyone who provides substantial contributions should receive appropriate recognition as an author or contributor when the manuscript is published.

10. INVESTIGATOR'S REGULATORY OBLIGATIONS

All clinical work conducted under this protocol is subject to 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 ^{18}F-AV-1451.

10.5. Investigational Product 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. 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. The files should include information such as visit dates, records of medical history, examinations administered, vital signs, 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.

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 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

Evaluations	Screen	Pre-dose	Dose	Continuous PET Imaging 20 minutes	End of Imaging	48 Hour Safety Follow-Up	Death
Signed Informed Consent[1]	X						
Demographics	X						
Medical / Disease History	X						
Concomitant Meds	X	X					
Cognitive Impairment Interview with Informant (IQCODE)	X						
Brain MRI	X						X
Physician Visit	X	X			X		
Vital Signs[2]	X	X			X		
[18]F-AV-1451 Administration			X				
PET Imaging				**Continuous 20 minute scan - 80 minutes after dose injection**			
Adverse Event Assessment	X	X	X	X	X	X	
Brain Harvesting							X

[1] Subjects should consent for clinical, imaging, and autopsy procedures at screening.

[2] Vital signs: pulse rate, respiratory rate, and supine blood pressure

INVESTIGATOR'S AGREEMENT TO PROTOCOL

Protocol ^{18}F-AV-1451-A13: "A High Resolution Autopsy Study Evaluating the Relationship of ^{18}F-AV-1451 PET Imaging and Tau Pathology"

Date and Version: 14Nov2016– Amendment 3

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

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

Principal Investigator:

_____

Printed Name

_____ _____

Signature Date