18F-AV-1451-A18 Protocol

An Open Label, Multicenter Study Evaluating the Imaging Characteristics of a Follow up 18F-AV-1451 Scan in Subjects That Participated in the Confirmatory Cohort of 18F-AV-1451-A05

NCT02795780

Approval date: 22 Mar 2016

Protocol Number: ^{18}F-AV-1451-A18

An open label, multicenter study evaluating the imaging characteristics of a follow up ^{18}F-AV-1451 scan in subjects that participated in the confirmatory cohort of ^{18}F-AV-1451-A05

Date and Version:

22 March 2016, Final

Name of Compound:

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

Sponsor:

Avid Radiopharmaceuticals, Inc.

Philadelphia, Pennsylvania USA

Approval/Signature:

[redacted]

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

Title of Study: ^{18}F-AV-1451-A18

An open label, multicenter study evaluating the imaging characteristics of a follow up ^{18}F-AV-1451 scan in subjects that participated in the confirmatory cohort of ^{18}F-AV-1451-A05

Planned number of subjects (Enrolled): Approximately 160

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

Dose*:* 370 MBq (10 mCi)

Route of Administration: Intravenous (IV) bolus

Study Phase: II

Study Centers: Approximately 25 centers in the United States

Trial Objectives:

The primary objective of this protocol is to assess longitudinal change of tau deposition as measured by ^{18}F-AV-1451 uptake over time.

Eligibility:

See Section 5.3, Selection of Subjects.

Study Design:

This is a phase 2 study that will evaluate longitudinal change of tau deposition as measured by ^{18}F-AV-1451 uptake over time. As subjects from the ^{18}F-AV-1451-A05 confirmatory cohort complete the ^{18}F-AV-1451-A05 study, they will be presented with the opportunity to participate in this longitudinal study.

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

Screening assessments should take place at the time of the subject's final ^{18}F-AV-1451-A05 study visit and will include safety labs (may be collected any time prior to ^{18}F-AV-1451 Injection), ECG, and collection of updated medical history and concomitant medications if not collected within last 30 days. An MRI, including both volumetric and standard clinical sequences will be conducted prior to the subject's ^{18}F-AV-1451 PET imaging session. Subjects

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

who qualify for the study will return to the clinic within 30 days of the screening visit for an ^{18}F-AV-1451 PET imaging session.

Assessments and Endpoints:

Each subject will have a screening visit(s), an MRI visit, an ^{18}F-AV-1451 PET imaging visit, and a follow-up phone call after the imaging visit.

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

For the ^{18}F-AV-1451 PET imaging session, subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of ^{18}F-AV-1451. At approximately 80 minutes post dose, a continuous 20-minute brain scan (4 acquisitions of 5-minute duration) will be obtained.

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

A follow-up phone call to the subject, or designated decision maker, will be conducted within 2 to 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day. Additional assessments that will be performed at each visit are detailed in Section 7.1.

Statistical Methods:

Descriptive statistics will be used to summarize the change in AV-1451 from A05 baseline (Change From Baseline; CFB) for the AV-1451 SUVR from the combination region and individual sub-regions. Analysis of covariance (ANCOVA) adjusting for baseline AV-1451 SUVR level and age will be applied to compare the least square (LS) mean tau CFB by clinical diagnosis groups (MCI vs. AD), amyloid status (AB+ vs. AB-) and the interaction of these two factors. The relationship between AV-1451 SUVR CFB and cognitive function assessments CFB will also be explored using ANCOVA models.

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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
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	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that

/Independent Ethics Committee	the safety, welfare and human rights of the subjects participating in a clinical study are protected.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	Intravenous
K_d	Dissociation Constant
MBq	Megabecquerel
mCi	Millicurie
MCI	Mild Cognitive Impairment
MHD	Maximum Human Dose
MRI	Magnetic Resonance Imaging
NOAEL	No Observable Adverse Effect Level
PET	Positron Emission Tomography
SUVr	Standard Uptake Value Ratio

1. INTRODUCTION

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

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

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

^{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 0.54 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; 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.

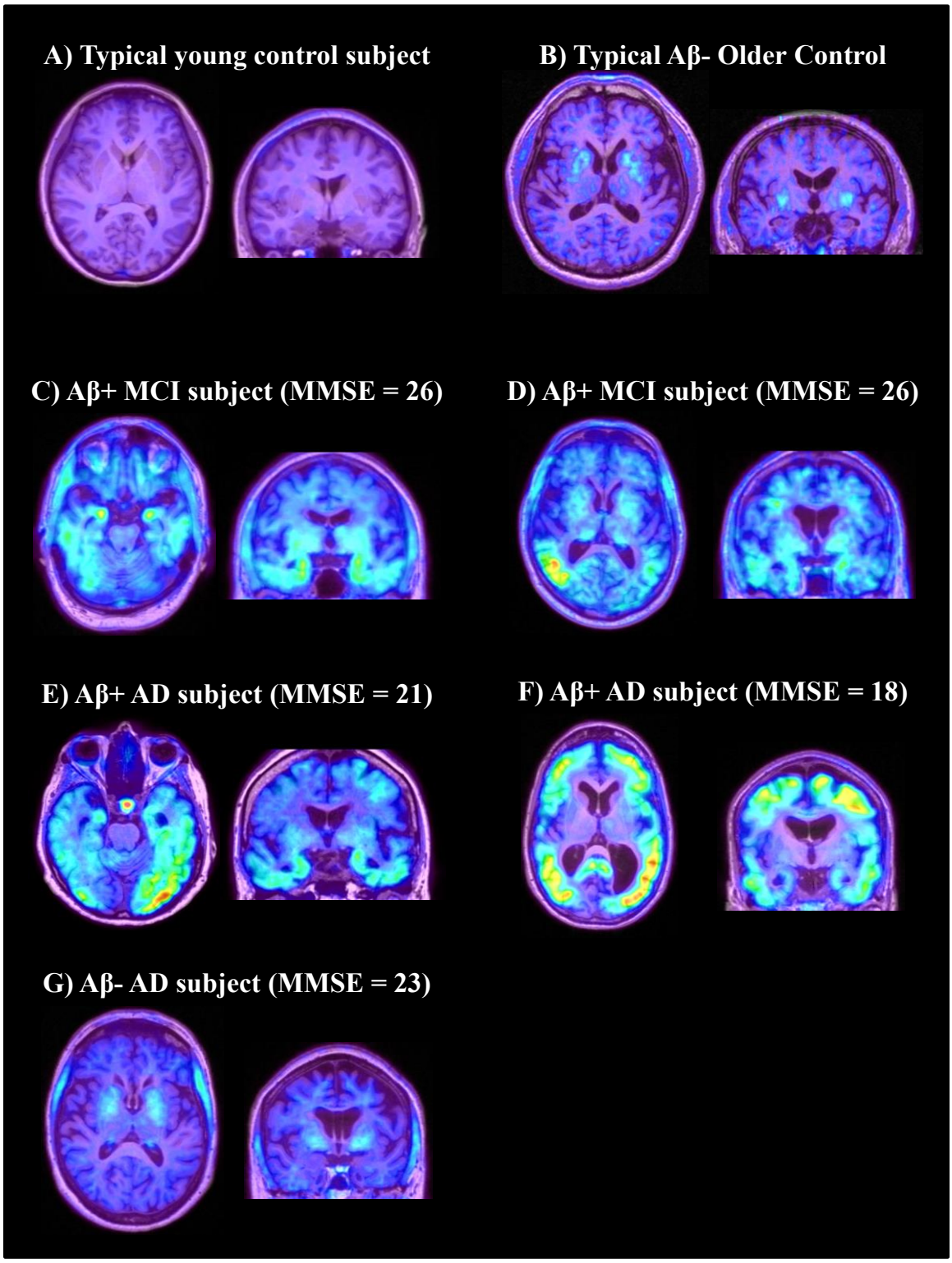
In vivo safety pharmacology studies were also conducted in rats to determine potential effects on the CNS and respiratory systems. In these studies no clinically relevant effects were reported at doses exceeding 100x the intended MHD. Additionally, non-radioactive AV-1451 has been tested in single and 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.

Three human clinical studies have been completed with ^{18}F-AV-1451. A total of 59 subjects have been exposed to ^{18}F-AV-1451 in these studies. The following side effects have been reported in clinical studies: diarrhea, headache, and altered taste. All reported events were mild in intensity and all subjects recovered from these events.

Evaluation of the PET images from completed studies demonstrates little focal cortical retention of ^{18}F-AV-1451 in either young cognitively normal (YCN) or older cognitively normal (OCN) subjects known to be amyloid negative (florbetapir PET SUVR <1.10; Figure 1 Panels A and B). However, OCN subjects frequently demonstrated retention in the mesial temporal lobes and some OCN subjects also demonstrated retention in the brainstem or striatum (Figure 1 Panel B). In MCI and AD subjects, retention appeared to spread from mesial temporal lobes to isocortical areas (Figure 1 Panels C-F). The pattern of ^{18}F-AV-1451 distribution seen on PET imaging, across subjects with various levels of impairment, paralleled the pattern reported in the classic autopsy series of older persons and subsequently used to define the Braak stage (Braak and Braak, 1991). Two clinically diagnosed AD subjects that were found to be amyloid negative on a florbetapir PET scan were the exception to this pattern, as their scans were similar to clinically normal elder controls and showed no cortical ^{18}F-AV-1451 retention (Figure 1 Panel G).

Figure 1: Representative ^{18}F-AV-1451 PET Scans



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 upper large intestinal wall (0.0955 ± 0.0134 mSv/MBq), the small intestine (0.0845±0.0118 mSv/MBq) and the liver (0.0572±0.00803 mSv/MBq). The Effective Dose was 0.0235 ± 0.0016 mSv/MBq. This results in an estimated Effective Dose of 8.70 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.

The overarching goal of this protocol is to further investigate the spectrum of PET imaging results with ^{18}F -AV-1451 in patients with cognitive decline. To accomplish this goal, the protocol will investigate longitudinal ^{18}F-AV-1451 results in patients with cognitive complaints ranging from mild cognitive impairment (MCI) to mild and moderate Alzheimer's disease (AD).

2. TRIAL OBJECTIVES

The primary objective of this protocol is to assess longitudinal change of tau deposition as measured by ^{18}F-AV-1451 uptake over time.

3. SPONSOR, INVESTIGATOR(S) AND OTHER PARTICIPANTS

The trial is sponsored by:

Avid Radiopharmaceuticals, Inc.

[redacted]

The medical contact is:

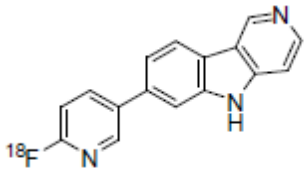
[redacted]

Approximately 25 centers in the United States 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 sterile, apyrogenic clear solution for intravenous bolus administration. ^{18}F-AV-1451 Injection contains ^{18}F-AV-1451 (drug substance) formulated in 10% (v/v) ethanol, USP in 0.9% sodium chloride injection, USP.

The shelf-life of ^{18}F-AV-1451 Injection is dependent on the strength or specific activity calculated at End-of-Synthesis (EOS) but is not more than 10 hours post EOS. The ^{18}F-AV-1451 Injection expiration time and date will be provided on the label on the secondary packaging of each vial or syringe.

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.

5. INVESTIGATIONAL PLAN

5.1. Overall Design and Plan of Trial

This is a phase 2 study that will evaluate longitudinal change of tau deposition as measured by ^{18}F-AV-1451 uptake over time. As subjects from the ^{18}F-AV-1451-A05 confirmatory cohort complete the ^{18}F-AV-1451-A05 study, they will be presented with the opportunity to participate in this longitudinal study.

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

Screening assessments should take place at the time of the subject's final ^{18}F-AV-1451-A05 study visit and will include safety labs (may be collected any time prior to ^{18}F-AV-1451 Injection), ECG, and collection of updated medical history and concomitant medications if not collected within last 30 days. An MRI, including both volumetric and standard clinical sequences will be conducted prior to the subject's ^{18}F-AV-1451 PET imaging session. Subjects who qualify for the study will return to the clinic within 30 days of the screening visit for an ^{18}F-AV-1451 PET imaging session.

Avid personnel will be blinded to the MRI and ^{18}F-AV-1451 PET scans performed on subjects with the exception of the following:

- Medical Director safety review, as necessary
- Periodic quality assurance (QA) assessments of a random subset of PET image data (not to exceed 20% unless issues identified that warrant additional review). These QA reviews will serve to ensure image quality and data integrity for the scans collected and managed by the imaging core laboratory. Avid staff performing the PET scan QA assessment will not be aware of diagnostic group or cognitive test scores for the subjects/images being reviewed.

Avid personnel will remain blinded to the MRI and ^{18}F-AV-1451 PET scans until the ^{18}F-AV-1451-A05 database lock.

^{18}F-AV-1451 PET Imaging Session(s):

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

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

5.2. Planned Dosage and Duration of Treatment

5.2.1. Dosage and Administration

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

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

Human dosimetry has been obtained in nine subjects. The results estimated an Effective Dose of 8.70 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 all of the following criteria are eligible to enroll in this trial:

1. Subjects who participated as a confirmatory subject in the ^{18}F-AV-1451-A05 study;
2. Subjects who completed the ^{18}F-AV-1451-A05 study;
3. Subjects who signed an IRB approved informed consent prior to any study procedures.

5.3.2. Exclusion Criteria

Subjects will be excluded from enrollment if they:

1. Have current clinically significant cardiovascular disease or clinically significant abnormalities on screening ECG;
2. A history of additional risk factors for Torsades de Pointes (TdP) (e.g., heart failure, hypokalemia, family history of Long QT syndrome) or are taking drugs that are known to cause QT-prolongation (a list of prohibited and discouraged medications is provided by the Sponsor);
3. Have a current clinically significant infectious disease, endocrine or metabolic disease, pulmonary, renal or hepatic impairment, or cancer that the investigator believes would affect study participation or scan results;
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 urine β-HCG within 24 hours prior to injection) or breastfeeding at screening. Females must agree to avoid becoming pregnant, and agree to refrain from sexual activity or to use reliable contraceptive methods for 24 hoursfollowing administration of ^{18}F-AV-1451 Injection. Males with female partners who are pregnant or of childbearing potential must agree to refrain from sexual activity for 24 hours following administration of ^{18}F-AV-1451 Injection. Additionally, males must agree not to donate sperm for 24 hours following administration of ^{18}F-AV-1451 Injection;
5. Have had a non-study related radiopharmaceutical imaging or treatment procedure within 7 days prior to the ^{18}F-AV-1451 imaging session;
6. Are receiving any investigational medications within the last 30 days;
7. In the opinion of the investigator, are otherwise unsuitable for this study.

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 in the electronic data capture (EDC) system.

5.5. Removal of Subjects from Trial

Subjects must be removed from the trial if:

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

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

5.6. Premature Termination of Trial/Closure of Center

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

6. WARNINGS/PRECAUTIONS

The most up-to-date and complete information regarding the use of ^{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. 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, vital signs, and ECGs

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 24 hours after administration of ^{18}F-AV-1451 Injection. ^{18}F-AV-1451 Injection must not be administered to females who are pregnant or lactating. Males with female partners who are pregnant or of childbearing potential must agree to refrain from sexual activity for 24 hours following administration of ^{18}F-AV-1451 Injection. Additionally, males must agree not to donate sperm for 24 hours following administration of ^{18}F-AV-1451 Injection.

7. PROCEDURES AND METHODS

7.1. Assessment Periods

See Section 11.2, Trial Flow Chart.

7.1.1. Screening Visit:

Screening assessments should take place at the time of the subject's final ^{18}F-AV-1451-A05 study visit. All screening assessments should be performed within 30 days of the initial ^{18}F-AV-1451 PET imaging session.

Screening assessments will include:

- Informed consent;
- Blood and urine samples will be collected for safety labs (may be collected any time prior to ^{18}F-AV-1451 Injection)
- ECG;
- Updated medical history and concomitant medications.

7.1.2. MRI Visit:

MRI should be acquired after subject consent is obtained, prior to the time of ^{18}F-AV-1451 Imaging Visit.

- MRI imaging including standard clinical sequences and volumetric MRI.

7.1.3. PET Imaging Visit:

It is preferable that the ^{18}F-AV-1451 PET Imaging Visit is performed within 30 days of the subject's final ^{18}F-AV-1451-A05 study visit, but no later than 3 months from the final ^{18}F-AV-1451-A05 study visit.

<u>^{18}F-AV-1451 PET Imaging Session:</u>

- A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to administration of ^{18}F-AV-1451 Injection to determine if they are still suitable to undergo the scan. If a designee performs this activity, a physician must be available to provide medical consultation;
- For women of childbearing potential, a negative urine pregnancy test must be obtained;
- Vital signs will be taken at the following time points:
  - immediately prior to administration of ^{18}F-AV-1451 Injection
  - after completion of the PET scan, prior to discharge;
- Subjects will receive a single IV bolus injection of approximately 370 MBq (10 mCi) +10% of ^{18}F-AV-1451 Injection followed by a saline flush. At approximately 80 minutes post dose, a continuous 20-minute brain scan (4 acquisitions of 5 minute duration) will be obtained.;
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected;

- The subject will be requested to void after completion of the PET scan;
- Adverse events will be continuously monitored during the ^{18}F-AV-1451 study imaging session; Subjects who experience an adverse event will not be discharged from the imaging center until the event has resolved or stabilized;
- A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge. If a designee performs this activity, a physician must be available to provide medical consultation; and a follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

7.2. Observations and Measurements

Informed Consent

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

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

Medical History

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

- Updated medical and surgical history
- Updated concurrent medications

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

MRI

MRI, including both volumetric and standard clinical sequences will be obtained. The MRI sequences and acquisition parameters will be described in a separate document.

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

Vital Signs

Vital signs (pulse rate, respiratory rate, and supine blood pressure) will be taken at the ^{18}F-AV-1451 imaging visit.

Electrocardiogram

- A resting 12-lead electrocardiogram will be recorded at Screening Visit.

Pregnancy Testing

- Urine beta hCG performed at the ^{18}F-AV-1451 imaging visit prior to injection for females of childbearing potential (defined as pre-menopausal, less than 2 years post-menopausal or not surgically sterile).

Physician Visit

A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must see the subject prior to drug administration and at study end, prior to discharge from the ^{18}F-AV-1451 imaging session. At this time, the physician should review all safety data and briefly examine/query the subject regarding potential adverse events or other treatment issues.

7.3. Protocol for Image Collection

Imaging manuals for both PET and MRI will be prepared by the respective core laboratories to include image acquisition parameters and transmission procedures.

7.4. Good Clinical Practice and Monitoring

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

This includes:

1. IRB/IEC approval: An investigation will be initiated at a study site only after the IRB/IEC for that study site has given their written approval of the protocol and informed consent;
2. Informed Consent: Study procedures will not be initiated until the subject and/or their legally authorized representative (as appropriate) signs the informed consent form;
3. Recording and monitoring of adverse events as outlined in Section 7.7.3 including the notification of study site clinical investigators, local IRBs and the FDA regarding serious adverse event;
4. Avid RP's obligation to monitor the participating center on a regular basis; and
5. The termination of a center or the trial if conditions apply, as outlined in Section 5.6.

7.5. Informed Consent and Subject Information

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

will explain all study procedures, risks, and alternative therapies. The subject and legally authorized representative will have an opportunity to have all questions answered by a physician. The subject will then sign and date the informed consent form, indicating willingness to participate in the study.

Subjects with AD are potentially a vulnerable population with compromised mental capacity. Investigators should take extra care to evaluate a patient's ability to give consent. If the subject is capable of giving informed consent then the subject should sign on the consent line of the informed consent form. When applicable the legally authorized representative should sign as well, indicating that they have witnessed the subject's consent, and further agree to participate as an informant.

If the subject is not capable of giving consent, consent may be given by a legally authorized representative. However, it is expected that all subjects entering this study should at least have the capacity to understand that they are engaging in a research study and should affirm that they do not object to participating, by signing on the Subject Assent line of the consent form. If the legal guardian is also the informant, the guardian must still sign the informant line of the form, indicating their own willingness to participate as an informant.

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

7.6. Documentation

^{18}F-AV-1451 PET scans, as well as MRI scans, will be saved in an appropriate electronic format as specified in the imaging manuals. A copy of all scans will be saved at the site/imaging center and a copy of each will be forwarded to the designated imaging core lab as described in the imaging manuals. All other data required by the protocol will be recorded in the CRF. All data in the CRF will be substantiated by "source documents," which consist of the subject's medical files, laboratory result sheets, ECG tracings, etc. All source documentation must be available to Avid and designees. Completed source documents and CRFs may need to be made available and complete for an audit by the FDA or other international regulatory authorities or Avid at any time. A ballpoint pen should be used to ensure that all copies are legible. CRFs and all other records must be filed in accordance with applicable laws and regulations (see Section 10.6)

7.7. Adverse Events (AE)

Avid's standards for recording and reporting adverse events (AEs) are to be followed regardless of applicable regulatory requirements that may be less stringent. All AEs must be fully recorded on the Adverse Event Page of the eCRF. Investigators will be instructed to report to Avid or its designee their assessment of the potential relatedness of each AE to investigational product or protocol procedure via electronic data entry. If a patient's treatment is discontinued as a result of an AE, study site personnel must clearly report to Avid or its designee via electronic data entry the circumstances and data leading to any

such discontinuation of treatment. In cases where the investigator notices an unanticipated benefit to the patient, study site personnel should report "unexpected benefit" with the actual event term to Avid or its designee (for example, the complete actual term would be "unexpected benefit- sleeping longer").

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

7.7.1. Adverse Event Monitoring

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

7.7.2. Adverse Event Definitions

Adverse Events

For reporting purposes, Avid will distinguish among pre-existing conditions, treatment - emergent adverse events and trial-emergent adverse events. Pre-existing conditions (i.e., undesirable experiences, signs or symptoms that begin prior to the Screening Visit) will be recorded on the medical history and/or physical exam eCRF pages. Signs and symptoms that are believed to be due to the pre-existing condition (started prior to dose of study medication) do not have to be recorded in the AEs section of the eCRF, unless there is an increase in frequency or severity. Additionally, signs or symptoms or changes in pre-exisiting conditions that occur outside the trial defined adverse event reporting period will be recorded in medical history.

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. For the purposes of this study, untoward medical occurrences will be considered associated with the use of ^{18}F-AV-1451, and thus be reported as adverse events, if they occur within 48 hours after ^{18}F-AV-1451 administration. Adverse events associated with the use of ^{18}F-AV-1451 injection will be recorded as treatment emergent. 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.

In order to capture possible adverse effects of trial participation, trial-emergent adverse events will also be reported as any untoward medical occurrences occurring between the time of consent and the time of imaging, but not during the 48 hour window following the administration of ^{18}F-AV-1451 injection.

The end of study for the purpose of adverse event reporting is defined as 48 hours after the 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.

Unexpected Adverse Event

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

Relationship to Investigational Product

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

Intensity/Severity of an Adverse Event

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

The following classifications should be used:

Mild:

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

Moderate:

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

Severe:

A severe adverse event is an adverse event that incapacitates the subject and prevents normal activities. Note that a severe event is not necessarily a serious event. Nor must a serious event necessarily be severe.

7.7.3. Adverse Event Documentation

All adverse events must be fully recorded on the Adverse Event Page via the Electronic Data Capture (EDC) system. Documentation must be supported by an entry in the subject file. Laboratory test, vital signs and ECG abnormalities considered by the Investigator to be clinically relevant should be reported on the Adverse Event page of the eCRF. Signs and symptoms of each AE should be described in detail (e.g., start and stop dates, severity/intensity, relationship to investigational product, action taken, and outcome).

Adverse events and laboratory test abnormalities fulfilling the definition of a serious adverse event should, in addition, be reported on the Serious Adverse Event Reporting Form.

7.7.4. Reporting of Serious Adverse Events

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

Serious adverse events occurring after a subject receive a dose of investigational product will be collected until 48 hours after the dosing of the investigational product, regardless of the investigator's opinion of causation. Therefore, SAEs that occur later than 48 hours after the dosing of the investigational product are not required to be reported unless the investigator feels the events were related to either investigational product or a protocol procedure.

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

8. STATISTICAL ANALYSIS

8.1. General Statistical Considerations

All statistical analyses will be performed using SAS® version 8.2 or higher.

Data will be summarized using descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, quartiles, minimum, and maximum) for continuous variables and using frequency count and percentage for discrete variables. The demographic and baseline characteristics data will be summarized according to clinical group (healthy volunteers and subjects with cognitive impairment) at recruitment for all subjects in the safety population. Safety data will be summarized for all patients.

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

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

8.1.1. Sample Size Estimation

This study is estimated to enroll about 100 subjects from A05 confirmatory arm. Current analyses with A05 exploratory arm data showed that for subjects met A05 confirmatory arm enrollment criteria (MCI or demented, MMSE between 20 and 27), AV1451 SUVR on average changed 0.0527 (SD=0.0970) for amyloid positive subjects at 9 months follow up. Assume a similar amyloid positivity to A05 exploratory arm (~60%), and assume the change of AV1451 SUVR is linear, this study is expected to have approximately 60 amyloid positive subjects and the mean change of AV1451 SUVR is expected to be 0.105, with a 95% confidence interval (0.0635, 0.1473).

8.2. Efficacy Analysis

The tau deposition measured as AV1451 SUVR values change from baseline (CFB) will be summarized by enrolling clinical diagnosis and amyloid status.

Analysis of covariance (ANCOVA) adjusting for baseline AV1451 SUVR and age will be applied to compare the least square (LS) mean SUVR CFB by clinical diagnosis groups, amyloid status and the interaction of two, through proper contrasts set up. The relationship between SUVR CFB and cognitive function assessments CFB will also be explored with ANCOVA models. The analysis details will be provided in statistical analysis plan (SAP).

Clinical and imaging data from the ^{18}F-AV-1451-A05 study will be made available to the ^{18}F-AV-1451-A18 study for these analyses once the database lock and unblinding has occurred for ^{18}F-AV-1451-A05 study.

8.3. Safety Analysis

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

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

Discontinuation

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

Laboratory Data

Subjects whose laboratory values are outside threshold values will be identified and tabulated.

Vital Signs

Vital signs measurements will be summarized by subject and by evaluation time point.

ECG

Any subjects showing QTc > 500 will be highlighted.

8.4. ^{18}F-AV-1451 Image Analysis

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

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

Additional analyses may explore various voxel and threshold based approaches.

9. USE OF DATA AND PUBLICATION

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

- We commit to timely communication of meaningful results of controlled clinical trials, regardless of outcome.
- As a sponsor, we may recommend that the Investigator(s) delay or decline publication in cases where the study design, conduct, or data are insufficient to allow meaningful interpretation. Avid and the Investigator(s) will discuss the study design and data in advance of the study, and again after completion, and will strive, through appropriate scientific debate, to reach a consensus regarding the potential merits of publication.
- Avid retains the right to review any manuscripts, presentations, or abstracts before they are submitted for publication. Where differences of opinion or interpretation exist regarding data planned for publication, the parties (Avid and the Investigator) should try to resolve them through appropriate scientific debate. Avid retains the right to delay publication for up to 60 days to protect intellectual property.

- Anyone who provides substantial contributions should receive appropriate recognition as an author or contributor when the manuscript is published.

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

10. INVESTIGATOR'S REGULATORY OBLIGATIONS

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

10.1. Institutional Review Board (IRB)

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

10.2. Informed Consent

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

10.3. Protocol Adherence

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

10.4. Documents Necessary for Initiation of the Trial

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

- Original signed and dated Statement of Agreement page;
- Copy of the IRB/IEC and radiation safety committee approval (if applicable);
- Copy of the IRB/IEC stamped approved consent form;
- Name and location of the laboratory utilized for laboratory assays, and other facilities conducting tests, including laboratory certification number and date of certification if available. Avid may be responsible for supplying these to the investigator if a central laboratory is used;

- List of reference range laboratory values. Avid may be responsible for this if a central laboratory is used; and
- Any additional licenses required in order to order to use ^{18}F-AV-1451.

10.5. Investigational Product Control

The receipt of clinical supplies (i.e. starting material for ^{18}F-AV-1451) must be documented at the site.

All drug supplies for this trial should be retained in a safe and secure place at all times during the trial. ^{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 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 or a designated Imaging Core Lab as specified in the Imaging Manual.

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

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

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

10.7. Adverse Events

All adverse events encountered during the clinical trial must be documented on the eCRF, whether or not considered drug-related.

Eli Lilly must be notified immediately (as soon as possible, and in all cases within 24 hours) of a drug experience, condition, development, or event, which is considered serious. Eli Lilly must be notified immediately of any findings with the use of the drug

that may suggest significant hazards, contraindications, adverse drug reactions (ADRs) and precautions pertinent to the safety of the drug. The investigator will be requested to complete a separate report form in addition to the information on the CRF. See section 7.7.4 for reporting serious adverse events

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

10.8. Records Retention

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

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

11. APPENDICES

11.1. References

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11.2. Trial Flow Chart

Evaluations	Screening Visit	MRI Visit	^{18}F-AV-1451 Imaging Visit	Follow-Up Phone Call
Updated Medical History	X		X	
Updated Concomitant Meds	X		X	
ECG	X			
Vital Signs			X	
Safety Labs[a]	X			
Urine Pregnancy Test			X	
MRI of the Brain		X		
PET Brain Scan			X	
Follow-up Phone Call				X
Evaluation by Physician/Designee	X		X	
Adverse Events	X	X	X	X
Serious Adverse Events	X	X	X	X

[a]Safety labs to be collected any time between consent and ^{18}F-AV-1451 Injection at Imaging Visit

INVESTIGATOR'S AGREEMENT TO PROTOCOL

Protocol: An open label, multicenter study evaluating the imaging characteristics of a follow up ^{18}F-AV-1451 scan in subjects that participated in the confirmatory cohort of ^{18}F-AV-1451-A05

Date and Version: 22 March 2016, Final

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