**Protocol Number: $^{18}$F-AV-1451-A08**

# $^{18}$F-AV-1451 PET Imaging in the Preclinical, Prodromal and Dementia Phases of Alzheimer's Disease

**Date and Version:**
28 February 2014

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

**Sponsor:**
Avid Radiopharmaceuticals
Philadelphia, Pennsylvania USA

**Approvals/Signatures and Date:**

[redacted]

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

**Title of Study:** $^{18}$F-AV-1451-A08

"$^{18}$F-AV-1451 PET Imaging in the Preclinical, Prodromal and Dementia Phases of Alzheimer's Disease"

**Planned number of subjects (Enrolled): Approximately 120**

This study will be divided into the following groups:

1. Approximately 25 cognitively healthy control subjects with no memory complaints
2. Approximately 25 subjects with subjective memory complaints (SMC) and a negative amyloid scan
3. Approximately 25 subjects with subjective memory complaints (SMC) and a positive amyloid scan
4. Approximately 25 subjects with mild cognitive impairment (MCI)
5. Approximately 20 subjects with Alzheimer's disease (AD)

Subjects will be recruited from the pool of participants participating in the Australian Imaging Biomarker and Lifestyle study of Ageing (AIBL).

**Name of compound and other imaging agents:** $^{18}$F-AV-1451([F-18]T807)

**Dose*:***
$^{18}$F-AV-1451 ([F-18]T807): 240 MBq $\pm$ 10%

**Route of Administration:** Intravenous (IV) bolus

**Study Phase:** I

**Study Centers:** Approximately 1 center in Australia

**Trial Objectives:**

***Primary Objective:***

1. To determine the level of total brain tau deposits in men and women aged over 60 years with objective cognitive impairment (MCI and AD) and without objective cognitive impairment (healthy controls and subjects with SMC).

***Exploratory Objectives:***

1. To determine the prevalence and distribution of brain tau in men and women aged over 60 years with and without subjective cognitive complaints.

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| Avid Radiopharmaceuticals | $^{18}$F-AV-1451([F-18]T807) | 7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole |

2. To relate the regional distribution of brain tau deposits to the presence of brain amyloid, current cognitive and brain function as well as brain atrophy.
3. To relate the change over time in the levels of regional brain tau to baseline brain tau, baseline brain amyloid and change over time in cognition and function, and brain volume.
4. To expand the $^{18}$F-AV-1451 safety database.

**Eligibility:**

Only subjects duly consented and enrolled in the AIBL study protocol will be considered for participation in this study. (See Section 5.3, Selection of Subjects)

**Study Design:**

This is a phase I study that will evaluate imaging characteristics of $^{18}$F-AV-1451 in the preclinical, prodromal and dementia phases of Alzheimer's disease.

AIBL subjects who have previously had beta-amyloid imaging in the form of florbetapir ($^{18}$F) Positron Emission Tomography (PET) imaging will be contacted to participate and must provide informed consent before starting any $^{18}$F-AV-1451-A08 study procedures. In addition to consenting to study procedures, participants will consent to have amyloid PET images and data, Magnetic Resonance Imaging (MRI) images and data, and cognitive data made available to this study to allow analysis and comparison. Other AIBL participants who have had other types of amyloid imaging will be recruited when required to reach the study target enrollment numbers. Screening assessments may take place over several days and will include demographic information and safety assessments.

Subjects who qualify for the study will return to the clinic at a later date for a $^{18}$F-AV-1451 PET scan. To optimally compare to the AIBL cognitive evaluation, the $^{18}$F-AV-1451 PET scan will be obtained within +/- 2 months of the planned (or obtained) cognitive evaluation in AIBL.

Subjects will have a follow-up $^{18}$F-AV-1451 PET scan at 12 (+/- 3) months following the initial $^{18}$F-AV-1451 scan. A brief cognitive evaluation will be performed on the day of the follow-up $^{18}$F-AV-1451 scan or on a separate visit within 2 months of the follow-up scan.

**Assessments and Endpoints:**

For each subject, the study will last for approximately 12 months. Participation will include 1 Screening Visit and up to 4 Study Visits (two $^{18}$F-AV-1451 PET imaging visits and if applicable, a MRI visit, and a follow-up cognitive assessment).

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

**Statistical Methods:**

Descriptive statistics and graphical displays by clinical diagnosis groups will be applied to describe the distribution of tau deposition as measured by $^{18}$F-AV-1451 uptake values. Analyses will be

| **Sponsor:** Avid Radiopharmaceuticals | **Name of Compounds:** $^{18}$F-AV-1451([F-18]T807) | **Active Ingredient(s):** 7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole |
|---|---|---|
| conducted to assess the relationship among tau deposition measurements, cognitive function measurements, and other collected biomarkers both cross-sectionally and longitudinally. | | |

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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. |
| **AIBL** | Australian Imaging Biomarker and Lifestyle study of Ageing |
| **ANCOVA** | Analysis of Covariance |
| **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 /Independent Ethics Committee** | A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare and human rights of the subjects participating in a clinical study are protected. |
| **Investigator** | A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. |
| **IV** | Intravenous |
| **$K_d$** | Dissociation Constant |
| **MBq** | Megabecquerel |
| **MCI** | Mild Cognitive Impairment |
| **MHD** | Maximum Human Dose |
| **MRI** | Magnetic Resonance Imaging |
| **NOAEL** | No Observable Adverse Effect Level |
| **PET** | Positron Emission Tomography |
| **SMC** | Subjective Memory Complaint |
| **SUVR** | Standard Uptake Value Ratio |
| **TGA** | Therapeutic Goods Administration |

# 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 (Duyckaerts et al., 1987; Brack et al., 2011; Nelson et al., 2012). 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 15 nM. A saturation binding experiment using purified Paired Helical Fragment-Tau isolated brains of AD patients yielded a $K_d$ value of 0.7 nM.

AV-1451 was assessed in competitive binding assays against a panel of 72 of the most common central nervous system (CNS) targets and no clinically relevant inhibition was seen. AV-1451 was positive in the i*n vitro* hERG assay; 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.

$^{18}$F-AV-1451 has been evaluated in two human studies under the exploratory IND (Chien, et. al.; 2013). Adverse events reported have been mild and transient; none have been considered related to $^{18}$F-AV-1451 administration. Preliminary evaluation of the PET images suggest that $^{18}$F-AV-1451 is eliminated from normal brain yielding only a diffuse pattern of background activity (Figure 1), whereas a regionally-specific gray matter distribution is observed in subjects with high probability AD (Figure 2).

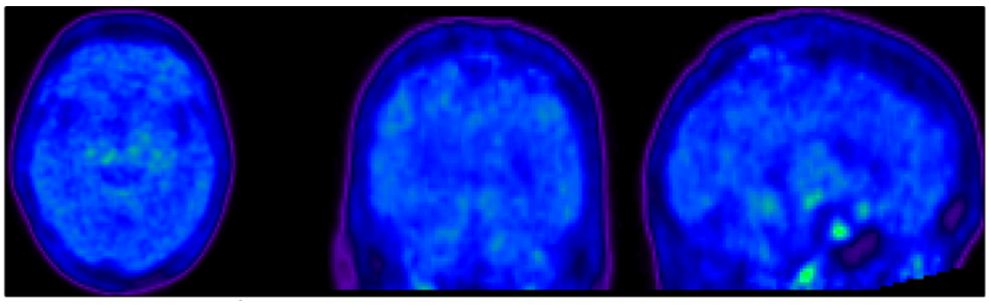


Figure 1: [redacted] female control subject (MMSE = 29)

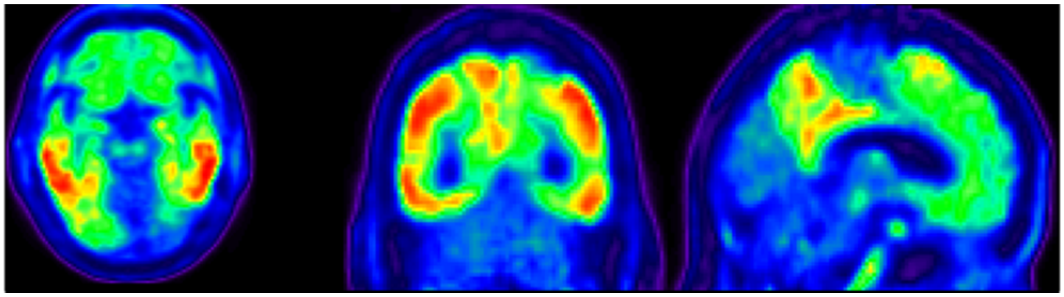


Figure 2: [redacted] male AD subject (MMSE = 18)

Human dosimetry has been obtained in nine subjects. Generally, the radiotracer distribution was consistent among the subjects and showed rapid hepatobiliary clearance. There were three organs that received estimated doses higher than 0.05 mSv/MBq. The organ that received the largest estimated dose was the upper large intestinal wall (0.0962 ± 0.0134 mSv/MBq), followed by the small intestine and the liver. The Effective Dose was 0.0241 ± 0.0016 mSv/MBq. This results in an estimated Effective Dose of 5.78 mSv for an anticipated 240 MBq injection and is comparable to the effective dose of approved $^{18}$F-labeled compounds such as fluorodeoxyglucose (FDG) and florbetapir F 18 injection.

The goal of this protocol is to further investigate the PET imaging results with $^{18}$F -AV-1451 in patients across the AD spectrum from individuals with subjective cognitive complaints to those with dementia. To accomplish this goal, the protocol will investigate $^{18}$F-AV-1451 results in older cognitively unimpaired individuals and across a spectrum of participants who may have increased brain tau deposition; a) normal older individuals, b) individuals with subjective cognitive complaints, c) with MCI and d) persons with dementia. The findings will be analysed in view of the brain amyloid status (typically using a florbetapir ($^{18}$F) PET scan), MRI scans and cognitive assessments performed in the same AIBL participants.

## 2. TRIAL OBJECTIVES

***Primary Objective:***

1. To determine the level of total brain tau deposits in men and women aged over 60 years with objective cognitive impairment (MCI and AD) and without objective cognitive impairment (healthy controls and subjects with SMC).

***Exploratory Objectives:***

1. To determine the prevalence and distribution of brain tau in men and women aged over 60 years with and without subjective cognitive complaints.
2. To relate the regional distribution of brain tau deposits to the presence of brain amyloid, current cognitive and brain function as well as brain atrophy.

3. To relate the change over time in the levels of regional brain tau to baseline brain tau, baseline brain amyloid and change over time in cognition and function, and brain volume.
4. To expand the $^{18}$F-AV-1451 safety database.

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

The trial is sponsored by:

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

The medical contact is:

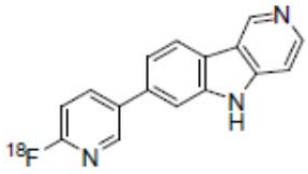
[redacted]

Approximately 1 center in Australia 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 ($\beta^+$) emission and has a half-life of 109.77 min. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron.

### 4.3 Decay Characteristics

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

| 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. $^{18}$F-AV-1451 Injection will be formulated in:

- a solution containing 10% (v/v) ethanol, USP in 0.9% sodium chloride injection, USP.

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

This is a phase I study that will evaluate imaging characteristics of $^{18}$F-AV-1451 in the preclinical, prodromal and dementia phases of Alzheimer's disease.

AIBL subjects who have previously had beta-amyloid imaging in the form of florbetapir ($^{18}$F) PET imaging will be contacted to participate and must provide informed consent before starting any $^{18}$F-AV-1451-A08 study procedures. In addition to consenting to study procedures, participants will consent to have amyloid PET images and data, MRI images and data, and cognitive data made available to this study to allow analysis and comparison. Other AIBL participants who have had other types of amyloid imaging will be recruited when required to reach the study target enrollment numbers. Screening assessments may take place over several days and will include demographic information and safety assessments.

Subjects who qualify for the study will return to the clinic at a later date for a $^{18}$F-AV-1451 PET scan. To optimally compare to the AIBL cognitive evaluation, the $^{18}$F-AV-1451 PET scan will be obtained within +/- 2 months of the planned (or obtained) cognitive evaluation in AIBL.

Subjects will have a follow-up $^{18}$F-AV-1451 PET scan at 12 (+/- 3) months following the initial $^{18}$F-AV-1451 scan. A brief cognitive evaluation will be performed on the day of the follow-up $^{18}$F-AV-1451 scan or on a separate visit within 2 months of the follow-up scan.

## 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 of approximately 240 MBq +/- 10% of $^{18}$F-AV-1451 Injection.

### *5.2.2 Rationale for Dosages*

Human dosimetry has been obtained in nine subjects. The results estimated an Effective Dose of 0.024 mSv/MBq and is comparable to the effective dose of approved $^{18}$F-labeled compounds such as FDG and florbetapir F 18 injection.

Compared with previous studies, reported in the Investigator's Brochure, which employed a 370 MBq dose, we propose a slightly lower dose in this trial in order to minimize the total amount of radiation potentially administered to patients, who may receive multiple doses of radiotracers during the course of

the AIBL study participation. Thus, for the purposes of this trial, $^{18}$F-AV-1451 will be administered IV in a radioactive dose of 240 MBq with an estimated Effective Dose of 6.2 mSv (including a nonclinical CT scan for attenuation correction). This dose is expected to have acceptable image quality in preliminary human studies. No treatment related adverse events have been reported using doses up to 370 MBq.

## 5.3 Selection of Subjects

### 5.3.1 Inclusion Criteria

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

1. Met all eligibility criteria for this cohort in the AIBL study protocol; and
2. Consented and currently enrolled in the AIBL study protocol with amyloid PET conducted or planned and MRI, cognitive and amyloid PET scan data can be made available to this study.

Subjects who meet the following criteria are eligible to enroll in the arm of this trial reserved for subjects with subjective memory complaints:

1. Met all eligibility criteria for this cohort in the AIBL study protocol; and
2. Consented and currently enrolled in the AIBL study protocol with amyloid PET conducted or planned and MRI, cognitive and amyloid PET scan data can be made available to this study.

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

1. Met all diagnostic and eligibility critiera for this cohort in the AIBL study protocol;
2. Consented and currently enrolled in the AIBL study protocol with amyloid PET conducted or planned and MRI, cognitive and amyloid PET scan data can be made available to this study; and
3. Have a reliable caregiver who is capable to provide correct information about the patient's clinical symptoms.

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

1. Met all diagnostic and eligibility criteria for this cohort in the AIBL study protocol;
2. Consented and currently enrolled in the AIBL study protocol with amyloid PET conducted or planned and MRI, cognitive and amyloid PET scan data can be made available to this study; and

3. Have a reliable caregiver who is capable to provide correct information about the patient's clinical symptoms.

Additionally, all subjects must meet all of the following criteria to be eligible to enroll in this trial:

1. Male or female English speaking subject > 60 years of age;
2. Have $\geq$ 7 years of education;
3. Have adequate visual and auditory acuity to complete neuropsychological testing;
4. Can tolerate PET imaging procedures;
5. Can tolerate MRI scan procedures;
6. Have the ability to provide informed consent for study procedures (If the subject is ineligible to give informed consent, based on local standards, the subject's legal representative may consent on behalf of the patient but the patient must still confirm assent).

### 5.3.2 Exclusion Criteria

All subjects will be excluded from enrollment if they:

1. Have a lifetime history of schizophrenia, schizoaffective disorder, or bipolar disorder;

2. Have a history of electroconvulsive therapy;

3. Have the presence of a metal device (e.g., any type of electronic, mechanical, or magnetic implant; cardiac pacemaker; aneurysm clips; implanted cardiac defibrillator) or potential ferromagnetic foreign body (metal slivers, metal shavings, other metal objects) that are contraindications for MRI;

4. Are claustrophobic or otherwise unable to tolerate the imaging procedure (use of mild sedatives are permitted to manage claustrophobia);

5. Have current clinically significant cardiovascular disease or clinically significant abnormalities on screening electrocardiogram (ECG) (including but not limited to QTc>450 msec);

6. A history of additional risk factors for Torsades de Pointes (TdP) (e.g., heart failure, hypokalemia, family history of Long QT syndrome) or are taking drugs that are known to cause QT-prolongation (a list of prohibited and discouraged medications is provided by the Sponsor);

7. Have a current clinically significant infectious disease, endocrine or metabolic disease, pulmonary, renal or hepatic impairment that the investigator believes would affect study participation (i.e. neuropsychological testing) or scan results;

8. Have a history of cancer (other than skin or in situ prostate cancer) within the previous 5 years;

9. Have current drug or alcohol abuse/dependence;

10. Have a history of alcohol abuse/dependence with 2 years of the onset of the symptoms of dementia;

11. 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 or breastfeeding at screening. Females must agree to avoid becoming pregnant, and both females and males must agree to refrain from sexual activity or to use reliable contraceptive methods for 90 days following administration of $^{18}$F-AV-1451 Injection; and

12. In the opinion of the investigator, are otherwise unsuitable for a study of this type.

### 5.4 Prior and Concomitant Therapy

Except as noted in the exclusion criteria, 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, including investigational medications that are continued from the start of the trial or that are started during the trial (other than the study medication) must be documented on the Concomitant Medication Page of the Case Report Form (CRF).

### 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 SAE 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/Contract Research Organization (CRO) monitors or to provide required access to data and source documents, staff turnover or inadequate staffing, and inadequate enrollment. Except in cases affecting subject safety, the investigator

may complete final study evaluations for ongoing subjects. In all cases of center or study termination, appropriate steps will be taken to ensure the safety of study subjects.

## 6. WARNINGS/PRECAUTIONS

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

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

## 7. PROCEDURES AND METHODS

### 7.1 Assessment Periods (See Section 11.2, Trial Flow Chart)

The study will consist of the following sequence of activities:

#### *7.1.1 Screening Visit:*

Subjects currently enrolled in the AIBL (previously had amyloid imaging in the form of florbetapir ($^{18}$F) PET imaging) study will be contacted to participate. Screening may take place over several days. All screening assessments should be performed within 60 days of the initial $^{18}$F-AV-1451 PET imaging session.

Screening assessments will include:

- Informed Consent;
- Demographics (age, gender, race, ethnicity, education, alcohol, drug use and smoking);
- Medical history and concomitant medications;
- Physical and neurological examination;
- Disease history (date/months since symptom onset, date/months since diagnosis) for cognitively impaired subjects;
- Family history of neurologic disease;
- Safety assessments: Vital signs (pulse rate, respiratory rate, supine blood pressure, height and weight), ECG, and safety labs (hematology, chemistry and urinalysis); and
- A physician will see the subject during the screening visit.

#### *7.1.2 MRI Visit*

MRI will be acquired within 6 months, either prior or after, the $^{18}$F-AV-1451 PET scan. The subject's AIBL MRI scan can be used as long as it is obtained within this timeframe.

### *7.1.3 $^{18}$F-AV-1451 PET Imaging Visits*

Initial $^{18}$F-AV-1451 PET Imaging Visit:
To optimally compare to the AIBL cognitive evaluation, the $^{18}$F-AV-1451 PET scan will be obtained within +/- 2 months of the planned (or obtained) cognitive evaluation in AIBL.

- A physician must see the subject prior to administration of $^{18}$F-AV-1451 Injection to determine if they are still suitable to undergo the scan;
- Vital signs will be taken (pulse rate, respiratory rate, supine blood pressure) at the following time points:
  - Immediately prior to administration of $^{18}$F-AV-1451 Injection (Weight will also be collected);
  - After completion of the 30-minute PET scan prior to discharge;
- Subjects will receive a single IV bolus injection target dose of 240 MBq +/- 10% of $^{18}$F-AV-1451 Injection followed by a saline flush;
- A 5-minute brain scan (1 frame of 5 minute duration) will begin immediately following the administration of $^{18}$F-AV-1451 (however if there are logistical or technical reasons this scan cannot obtained, it will not be a protocol violation);
- At approximately 75 minutes following injection, a continuous 30-minute brain scan (6 frames of 5 minute duration) will begin;
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected;
- Adverse events will be continuously monitored during the $^{18}$F-AV-1451 PET imaging visit. Subjects who experience an adverse event will not be discharged from the imaging center until the event has resolved or stabilized;
- A physician will see the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge; and
- A follow-up phone call to the subject, or designated decision maker, will be conducted within 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

Follow-Up $^{18}$F-AV-1451 PET Imaging Visit:
Subjects will have a follow-up $^{18}$F-AV-1451 PET scan at 12 (+/- 3) months following the initial $^{18}$F-AV-1451 scan.

- A physician must see the subject prior to administration of $^{18}$F-AV-1451 Injection to determine if they are still suitable to undergo the scan;

- Vital signs will be taken (pulse rate, respiratory rate, supine blood pressure) at the following time points:
  - Immediately prior to administration of $^{18}$F-AV-1451 Injection (Weight will also be collected);
  - After completion of the 30-minute PET scan prior to discharge;
- Subjects will receive a single IV bolus injection target dose of 240 MBq +/- 10%) of $^{18}$F-AV-1451 Injection followed by a saline flush;
- A 5-minute brain scan (1 frame of 5 minute duration) will begin immediately following the administration of $^{18}$F-AV-1451 (however if there are logistical or technical reasons this scan cannot obtained, it will not be a protocol violation);
- At approximately 75 minutes following injection, a continuous 30-minute brain scan (6 frames of 5 minute duration) will begin;
- The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected;
- Adverse events will be continuously monitored during the $^{18}$F-AV-1451 PET imaging visit. Subjects who experience an adverse event will not be discharged from the imaging center until the event has resolved or stabilized;
- A physician will see the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge; and
- A follow-up phone call to the subject, or designated decision maker, will be conducted within 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.
- A brief cognitive evaluation will be performed on the day of the follow-up $^{18}$F-AV-1451 scan. If not able to be done on the day of scan it may be done on a separate visit within 2 months of the follow-up scan. The brief cognitive evaluation will consist of the Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR) scale, the alternative forms of California Verbal Learning Test-II (CVLT-II), Delis-Kaplan Executive Function System (D-KEFS) verbal fluency (letter and category), Boston Naming Test 30 Item, (Taylor) Complex Figure Test and Logical Memory – Wechsler Memory Scale – Revised.

## 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 the 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/Independent Ethics Committee (IRB/IEC) prior to use.

Medical History, Neurologic Disease History

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

- Relevant demographic information
- Review of body systems
- Social history
- Medical and surgical history
- Concurrent medications
- Neurologic Disease history (date/months since symptom onset and date/months since diagnosis)
- Family history of neurologic disease

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

Physical Examination

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

Neurological Examination

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

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

Vital Signs

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

- $^{18}$F-AV-1451 Imaging Visit
    - Immediately prior to the administration of $^{18}$F-AV-1451 Injection
    - After the completion the 30-minute PET scan prior to discharge.

Height and Weight

At both screening and imaging visits (immediately prior to each $^{18}$F-AV-1451 administration) body weight will be measured, lightly clothed. Height will only be measured at screening.

Electrocardiogram (ECG)

A resting 12-lead electrocardiogram will be recorded as part of the screening visit.

Clinical Laboratory Tests

Clinical laboratory evaluation will be performed at screening.

Tests will include:

- **Hematology** (5 mL EDTA): hemoglobin, hematocrit, RBC, WBC, MCH, MCHC, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelets, morphology, MCV, and RBC morphology.

- **Chemistry** (6 mL blood): total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), urea nitrogen, creatinine, glucose, uric acid, calcium, phosphorus, total protein, albumin, total cholesterol, triglycerides, sodium, potassium, bicarbonate, chloride, magnesium, globulin, GGT.

- **Urinalysis** (10 mL, urine): Samples will be used to assess glucose, RBC, WBC, specific gravity, pH, protein, ketones, urobilinogen, blood, nitrite, microscopic, color, bilirubin, casts, epithelial cells, leukocyte, esterase, and bacteria.

Neuropsychological Testing

A brief cognitive evaluation will be performed on the day of the follow-up $^{18}$F-AV-1451 scan or on a separate visit within 2 months of the follow-up scan. The brief cognitive evaluation will consist of the MMSE (Folstein et al., 1975), CDR (Morris et al., 1993), the alternative forms of California Verbal Learning Test-II (CVLT-II) (Delis et al., 2000), D-KEFS verbal fluency (letter and category) (Delis et al., 2001), Boston Naming Test (BNT) 30 Item (Saxton et al., 2000), (Taylor) Complex Figure Test (Hamby et al., 1993) and Logical Memory – Wechsler Memory Scale – Revised (Wechsler, 1987).

Physician Visit

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

### 7.3 Protocol for Image Collection

The sponsor will prepare and distribute imaging manuals for $^{18}$F-AV-1451 imaging parameters and scan transmission procedures prior to site initiation. The MRI, if applicable, imaging parameters should follow the Alzheimer's Disease Neuroimaging Initiate (ADNI) MRI protocol.

### 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/IECs and the FDA, TGA or other international regulatory authorities 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.

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.

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 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 IRB/IEC. 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 and MRI scans will be saved in an appropriate electronic format as specified in the imaging manuals. A copy of all scans, including the florbetapir ($^{18}$F) and MRI scans conducted in the AIBL study protocol, 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 eCRFs. All data in the eCRFs will be substantiated by "source documents," which consist of the subject's medical files, laboratory result sheets, ECG tracings, etc. All source documentation must be available to Avid and designees. Completed source documents and eCRFs may need to be made available and complete for an audit by the FDA or other international regulatory authorities or Avid at any time. CRFs and all other records must be filed in accordance with applicable laws and regulations (see Section 10.6)

### 7.7 Adverse Events (AE)

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

Laboratory test abnormalities considered by the Investigator to be clinically relevant should be reported on the adverse event eCRFs. Signs and symptoms of each AE should be described in detail (e.g., start and stop dates/time,

severity/intensity, relationship to study drug, action taken, and outcome). Additionally, any clinically significant findings from laboratory evaluations, vital sign measurements, or other study procedures including those that result in a diagnosis should be reported as an AE to Avid or its designee**.**

### *7.7.1 Adverse Event Monitoring*

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

### *7.7.2 Adverse Event Definitions*

Adverse Events

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

For reporting purposes, Avid will distinguish among pre-existing conditions, trial-emergent adverse events and treatment-emergent adverse events.

Pre-existing conditions (i.e., undesirable experiences, signs or symptoms that begin prior to the Screening Visit) will be recorded on the medical history and/or physical exam eCRF pages. During the study, site personnel will record any change in the condition(s) and occurrence and nature of any AEs. Signs and symptoms that are believed to be due to the pre-existing condition under study (started prior to dose of study medication) do not have to be recorded in the AEs section of the eCRF, unless there is an increase in frequency and 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 administration of $^{18}$F-AV-1451. Adverse events associated with the use of $^{18}$F-AV-1451 will be recorded as treatment emergent relative to the respective drug. 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, during the study period but not during the 48 hour window following the administration of $^{18}$F-AV-1451. For the purpose of trial-emergent adverse events, the study period will be defined as beginning with the signing of consent and ending immediately before the administration of $^{18}$F-AV-1451.

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 Study Drug

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

Intensity/Severity of an Adverse Event

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

The following classifications should be used:

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

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

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

### *7.7.3 Adverse Event Documentation*

All adverse events must be fully recorded on the adverse event eCRFs. Documentation must be supported by an entry in the subject file. Laboratory test, vital signs and ECG abnormalities considered by the Investigator to be clinically relevant should be reported on the adverse event eCRFs. Signs and symptoms of each AE should be described in detail (e.g., start and stop dates/time, severity/intensity, relationship to study drug, action taken, and outcome).

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

### *7.7.4 Reporting of Serious Adverse Events*

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

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

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

study.

# 8. STATISTICAL ANALYSIS

## 8.1 General Statistical Considerations

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

The study data collected under AIBL protocol, such as but not limited to subjects' demographic and baseline characteristics, history taking, clinical assessments, neuropsychological evaluations, florbetapir ($^{18}$F) and MRI scan will be transferred to study investigator and study sponsor (Avid) for analysis purpose.

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 according to clinical group. 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.

## 8.2 Sample size estimation

Due to the exploratory purpose of this study, the sample size was determined outside statistical consideration.

## 8.3 Image Analysis

All $^{18}$F-AV-1451 PET images obtained starting at 75 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 for the following objectives.

Mean, standard deviation, minimum and maximum of the SUVR values for all groups will be calculated.

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

## 8.4 Primary objective analysis

Descriptive statistics will be applied to summarize the tau deposition as measured by $^{18}$F-AV-1451 uptake values by clinical enrollment groups. Box-and-Whiskers plots by clinical enrollment groups will be created to describe the tau deposition

distributions. ANOVA test will be applied to compare the tau deposition between subjects with objective cognitive impairment (MCI and AD) and subjects without objective cognitive impairment (healthy controls and subjects with SMC) at baseline, and at 12 months follow up visit. If the pre-requisites of ANOVA are not met then appropriate non parametric test such as Kruskal-Wallis test will be applied.

### 8.5 Analysis of exploratory objectives

Analysis covariance (ANCOVA) models will be applied to compare the change from baseline values in tau deposition as measured by $^{18}$F-AV-1451 uptake across clinical diagnosis groups and amyloid status, adjusting for baseline value and baseline age. If the prerequisites of ANCOVA model are met non-parametric tests such as rank ANCOVA (RANCOVA) will be applied instead.

Based on data availability, the change in tau deposition (as measured by $^{18}$F-AV-1451 uptake) during the 12 months follow up period will be correlated to change in cognitive function measurements and other collected biomarkers during the same follow up period.

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

### 8.6 Safety Analysis

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

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

<u>Discontinuation</u>

All subjects who discontinued 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

Changes in vital signs from baseline will be summarized.

ECG

Any subjects showing QTc > 500 will be highlighted.

## 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 single center study. A single center publication, reporting the primary analysis data set, should precede any other publications.

## 10. INVESTIGATOR'S REGULATORY OBLIGATIONS

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

### 10.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

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 or $^{18}$F-AV-1451.

### 10.5 Study Drug 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 to Avid or a designated Imaging Core Lab as specified in the Imaging Manual.

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

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

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

## 10.7 Adverse Events

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

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

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

### 10.8 Records Retention

All correspondence (e.g., with Avid, IRB/IEC, etc.) relating to this clinical trial should be kept in appropriate file folders. Records of subjects, source documents, and drug inventory sheets pertaining to the trial must be kept on file. Records must be retained until the date a marketing application (NDA) is approved for the drug for the indication for which it is being investigated, or until 2 years following the date of clinical trial termination or completion, whichever is later. If no application is to be filed or if the application is not approved for such indication, records should be kept until 2 years following the date of clinical trial termination or completion.

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

# 11. APPENDICES

## 11.1 References

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## 11.2 Trial Flow Chart

| | | Initial and Follow-Up[h] $^{18}$F-AV-1451 Imaging Visits | | | | |
|---|---|---|---|---|---|---|
| **Evaluations** | **Screening Visit[a]** | **Pre-Dose** | **Immediately after injection** | **75-105 minutes post-injection** | **End of $^{18}$F-AV-1451 Imaging (prior to discharge)** | **Follow-up Phone Call[g]** |
| Signed Informed Consent | X | | | | | |
| Demographics | X | | | | | |
| Medical History/Neurologic Disease History | X | | | | | |
| Concomitant Meds | X | | | | | |
| Physical/Neurological Exam | X | | | | | |
| ECG | X | | | | | |
| Vital Signs | X[b] | X[c] | | | X[d] | |
| Safety Labs | X | | | | | |
| MRI[e] | | | | | | |
| PET Brain Scan | | | X[f] | X | | |
| Evaluation by a physician | X | X | | | X | |
| Adverse Events | X | X | X | X | X | X |
| Serious Adverse Events | X | X | X | X | X | X |

a. Screening may take place over several days. All assessments must be performed within 60 days of the initial $^{18}$F-AV-1451 imaging visit.
b. Screening vital signs include, pulse rate, respiratory rate, supine blood pressure, height and weight.
c. Vital signs include pulse rate, respiratory rate, supine blood pressure, and weight.
d. Vital signs include pulse rate, respiratory rate, and supine blood pressure.
e. Will be acquired within 6 months, either prior or after, the $^{18}$F-AV-1451 PET scan. The subject's AIBL MRI scan can be used as long as it is obtained within this timeframe.
f. A 5-minute brain scan (1 frame of 5 minute duration) will begin immediately following the administration of $^{18}$F-AV-1451. However, if there are logistical or technical reasons this scan cannot obtained, it will not be a protocol violation.
g. Conducted within 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events.
h. A brief cognitive evaluation will be performed on the day of the follow-up 18F-AV-1451 scan or on a separate visit with 2 months of the follow-up scan. It will consist of the MMSE, CDR, the alternative forms of CVLT-II, D-KEFS verbal fluency (letter and category), Boston Naming Test 30 Item, (Taylor) Complex Figure Test and Logical Memory – Wechsler Memory Scale – Revised.

## INVESTIGATOR'S AGREEMENT TO PROTOCOL

**Protocol $^{18}$F-AV-1451-A08:** "$^{18}$F-AV-1451 PET Imaging in Preclinical, Prodromal and Dementia Phases of Alzheimer's Disease"

**Date and Version**: 28 February 2014

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