PROTOCOL NUMBER: ^{18}F-AV-1451-A19

^{18}F-AV-1451 PET Imaging in Subjects with Frontotemporal Dementia

DATE AND VERSION:

05 MAY 2016, FINAL

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

Sponsor:
Avid Radiopharmaceuticals
Philadelphia, Pennsylvania USA

[redacted]

Sponsor: Avid Radiopharmaceuticals	**Name of Compound:** ^{18}F-AV-1451([F-18]T807)	**Active Ingredient(s):** 7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole
Title of Study: ^{18}F-AV-1451-A19 "^{18}F-AV-1451 PET Imaging in Subjects with Frontotemporal Dementia"		
Planned number of subjects (Enrolled): Approximately 25 Subjects diagnosed by a dementia specialist with a clinical Frontotemporal Dementia (FTD) syndrome and expected tau or TDP-43 pathology.		
Name of compound: ^{18}F-AV-1451([F-18]T807) **Dose*:*** 370 MBq (10 mCi) **Route of Administration:** Intravenous (IV) bolus		
Study Phase: I		
Study Centers: Approximately 3 centers in the United States		
Trial Objectives: The primary objective of this study is: • To evaluate ^{18}F-AV-1451 retention in PET scans of FTD subjects. A secondary objective of this study is: • To expand the ^{18}F-AV-1451 safety database.		
Eligibility: 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 subjects with Frontotemporal Dementia (FTD). Subjects followed in a referral center research cohort for FTD will be contacted to participate and must provide informed consent before starting any ^{18}F-AV-1451-A19 study procedures. Screening assessments may take place over several days and will include demographic information, a medical assessment for eligibility, ECG, a brief cognitive assessment (e.g. MMSE), and florbetapir F 18 Positron Emission Tomography (PET) imaging. The screening florbetapir F 18 PET scan is to be performed to assess for evidence of amyloid pathology and should be interpreted by a local reader prior to enrollment. Subjects will receive a single IV bolus injection of approximately 370 MBq		

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

(10 mCi) +10% of florbetapir F 18 followed by a saline flush. A 20-minute continuous, dynamic PET brain scan will begin approximately 50 minutes following the dose administration;

Subjects who qualify for the study will come to the imaging center at a later date and will have a catheter(s) placed for IV administration of ^{18}F-AV-1451. Vital signs will be taken in a supine position immediately prior to administration of ^{18}F-AV-1451 (within 30 minutes prior to injection) and at the completion of imaging prior to subject discharge. Subjects will receive a single IV bolus injection of approximately 370 MBq (10 mCi) ^{18}F-AV-1451 followed by a saline flush. A 30 minute dynamic image will begin approximately 75 minutes following the dose administration.

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

A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days, but not less than 48 hours, after each imaging visit, to confirm subject well-being and to collect information about any new adverse events.

Assessments and Endpoints

Details of the assessments that will be performed at each visit are detailed in Section 7.1. Subjects will complete the following:

- Screening Visit, including florbetapir F 18 PET imaging
- ^{18}F-AV-1451 PET Imaging Visit
- Follow-up Phone Calls

Tracer uptake in subjects will be evaluated by both qualitative and quantitative techniques.

Statistical Methods:

Descriptive Statistics will be used to summarize the clinical characteristics and the ^{18}F-AV-1451 uptake. The pattern of ^{18}F-AV-1451 tracer binding will be measured both by qualitative visual analysis and by SUVr.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

Aβ	Beta amyloid
AD	Alzheimer's disease
ADR	Adverse Drug Reaction
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.
amu	Atomic mass unit
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
β+	Beta decay
bvFTD	Behavioral variant Frontotemporal Dementia
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.
CI	Confidence Interval
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.
ECG	Electrocardiogram
Efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.
EOS	End of Synthesis
FDA	US Food and Drug Administration

FDG	^{18}F – Fluorodeoxyglucose
FTD	Frontotemporal Dementia
GCP	Good Clinical Practice
hERG	human Ether-à-go-go-Related Gene
IB	Investigator's Brochure
ICF	Informed Consent Form
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
keV	Kiloelectronvolt
LAR	Legally authorized representative
MBq	Megabecquerel
mCi	Millicurie
MedDRA	Medical Dictionary for Regulatory Activities
MHD	Maximum Human Dose
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
mSv	Millisivert, a derived unit of ionizing radiation dose in the International System of Units
MW	Molecular weight
N	Number, or total

NDA	New Drug Application
NLT	Not Less Than
NORM-JECT®	syringes which are latex-free, contain no rubber, no silicone oil, styrene or DEHP and are DNA-free
NOAEL	No Observable Adverse Effect Level
PET	Positron Emission Tomography
PHF tau	Paired Helical Filament tau
PhRMA	Pharmaceutical Research and Manufacturers of America
PSP	Progressive supranuclear palsy
v/v	Percentage solution
QT	A measure of the time between the start of the Q wave and the end of the T wave
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
Serious Adverse Event (SAE)	A SAE is an AE that results in one of the following outcomes or constitutes one of the following events: death, initial or prolonged inpatient hospitalization, life-threatening experience (that is, immediate risk of dying); Persistent or significant disability/incapacity; congenital anomaly/birth defect; considered significant by the investigator for any other reason.
SOC	System organ class
SOP	Standard Operating Procedure
SUVr	Standard Uptake Value Ratio
TdP	Torsades de Pointes

1. INTRODUCTION

The clinical diagnosis of patients with dementia is challenging and is frequently inaccurate compared to pathological diagnosis at autopsy. Although Alzheimer's disease (AD) is the most common cause of dementia, other etiologies including Fronto-Temporal Dementia (FTD), vascular dementia and Dementia with Lewy Bodies occur in a substantial number of cases, (Barker et al. 2002) and there may be substantial overlap in the clinical presentation of these disorders. In clinico-pathological studies, 10 - 20% of patients diagnosed with AD in life did not have pathology consistent with the disease at autopsy (Lim et al. 1999, Mayeux et al. 1998, Ranginwala et al. 2008). Conversely, a recent study showed that 40% of dementia patients diagnosed with a disorder other than AD by an expert neurologist in life had AD pathology (i.e., AD or mixed dementia) on post mortem examination (Beach et al. 2012).

Accurate antemortem diagnosis can be particularly challenging in FTD given the clinical and pathologic heterogeneity of the disease (Rabinovici and Miller 2010). Most cases of FTD can be classified into two major pathologic categories: (1) diseases that involve tau deposition (FTD-Tau) and (2) conditions associated with tau-negative, ubiquitin and TDP43-positive inclusions (FTD-TDP) (Mackenzie et al. 2010). In a minority of cases, FTD-Tau can be predicted during life with high accuracy based on the presence of a known mutation in the MAPT gene, or based on a highly correlated clinical phenotype (e.g. progressive supranuclear palsy (PSP) - Richardson's Syndrome) (Josephs et al. 2006). However, the relationships between other FTD clinical phenotypes and pathologic subtypes are far less predictable (Forman et al. 2006, Hodges et al. 2004, Josephs et al. 2011, Kertesz et al. 2005). For example, the underlying histopathology in patients with behavioral-variant FTD (bvFTD), the most common clinical FTD syndrome, is split equally between FTD-Tau and FTD-TDP (Josephs et al. 2011) and there are currently no known reliable methods to distinguish the two during life. Accurately determining the underlying neuropathology during life is a critical need to enhance the development and testing of biologically specific drugs targeting tau or TDP.

^{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 PHF 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.

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 (0.0955 ± 0.0134 mSv/MBq), followed by the small intestine and the liver. 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.

^{18}F-AV-1451 may be useful as a marker of tau pathology in patients with AD and other neurodegenerative disorders. Several preliminary studies using ^{18}F-AV-1451 have been completed (e.g., Chien et al., 2013). The purpose of the current study is to extend these findings by evaluating the usefulness of AV-1451 in FTD and in particular, whether the regional pattern of tau deposition typical of AD is present in FTD cases.

2. TRIAL OBJECTIVES

Trial Objectives:

The primary objective of this study is:

- To evaluate ^{18}F-AV-1451 retention in PET scans of Frontotemporal Dementia (FTD) subjects.

A secondary objective of this study is:

- 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:

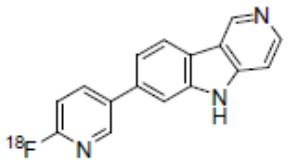
[redacted]

Approximately 3 centers in the United States will participate in this trial.

4. TEST DRUG AND CONTROL AGENTS

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

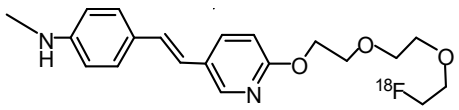
7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole



MW = 262.27 amu

4.2. Descriptive Name: Florbetapir F 18

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



^{18}F-AV-45

MW= 359.4 amu

4.3. Radioactive Labeling

The compounds are 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.

4.4. 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.

4.5. 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.

4.6. Formulation and Dose Florbetapir F 18 Injection

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

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

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

^{18}F-AV-1451 Injection is contained in a sterile, non-pyrogenic septum sealed Type I glass vial or a sterile apyrogenic syringe. Vials and syringes containing ^{18}F-AV-1451 Injection are stored in an opaque shield (secondary packaging) which protects personnel from radiation exposure. The shield may be packaged in a Type A shipping container for shipment to the imaging facility.

4.8. Packaging Florbetapir F 18 Injection

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

4.9. 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.

4.10. Storage and Handling Florbetapir F 18 Injection

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

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 subjects with Frontotemporal Dementia (FTD).

Subjects followed in a referral center research cohort for FTD will be contacted to participate and must provide informed consent before starting any ^{18}F-AV-1451-A19 study procedures. Diagnosis be will determined by companion study with detailed characterization provided by enrolling physician. Screening assessments may take place over several days and will include demographic information, a medical assessment for eligibility, ECG a brief cognitive assessment (e.g. MMSE), and florbetapir F 18 Positron Emission Tomography (PET) imaging. The screening florbetapir F 18 PET scan is to be performed to assess for evidence of amyloid pathology and should be interpreted by the local reader prior to enrollment.

Subjects who qualify for the study will come to the imaging center at a later date and will have a catheter(s) placed for IV administration of ^{18}F-AV-1451. Vital signs will be taken in a supine position immediately prior to administration of ^{18}F-AV-1451 (within 30 minutes prior to injection) and at the completion of imaging prior to subject discharge. Subjects will receive up to a target dose of 370 mBq as a single IV bolus of ^{18}F-AV-1451. A 30 minute dynamic image starting approximately 75 minutes post injection will be obtained.

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

A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 or 3 business days, but not less than 48 hours, after each imaging visit, to confirm subject well-being and to collect information about any new adverse events.

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 370 MBq (10 mCi) of ^{18}F-AV-1451 Injection.

Florbetapir F 18:

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

5.2.2. Rationale for Dosage

^{18}F-AV-1451 will be administered IV in a radioactive dose of 370 MBq with a maximum human dose (MHD) limited to 20 μg of compound by weight.

The Effective Dose of 8.70 mSv for a 370 MBq (10 mCi) injection 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 previous human studies.

5.3. Selection of Subjects

Approximately 25 subjects will be enrolled.

5.3.1. Inclusion Criteria

Subjects diagnosed by a dementia specialist with symptomatic clinical syndromes with expected Frontotemporal Dementia pathology will be enrolled. Clinical syndromes associated with FTD pathology include: behavioral-variant FTD, FTD with motor-neuron disease, non-fluent/agrammatic and semantic variants of primary progressive aphasia, progressive supranuclear palsy syndrome and corticobasal syndrome. Symptomatic carriers of a known autosomal dominant gene mutation associated with FTD, including: MAPT, GRN, C9ORF72, TARDP, CMP2B, VCP, FUS as well as non-gene carriers are eligible for enrollment.

Diagnosis will be determined by companion study with detailed characterization provided by enrolling physician.

Subjects who are identified with one of the above clinical syndromes of FTD pathology and meet all of the following criteria are eligible to enroll in this trial:

1. Male or female subjects at least 18 years of age;

2. Subjects who give informed consent or have a legally authorized (LAR) to consent for study procedures.
3. Subjects who have volumetric brain MRI images obtained as part of the site's companion protocol within one year of enrollment available for submission to Avid. (If the subject does not have a prior MRI available for submission to Avid, an MRI may be conducted under this protocol if the subject is able to tolerate one.); and
4. Subjects who in the opinion of the investigator can tolerate the PET scan procedures.

5.3.2. Exclusion Criteria

1. Have clinically significant cardiac, hepatic, renal, pulmonary, metabolic, or endocrine disturbances as indicated by history, which in the opinion of the investigator might pose a potential safety risk to the subject;
2. Have a history of risk factors for Torsades de Pointes (TdP) (e.g., hypokalemia, family history of Long QT syndrome), including clinically significant findings on ECG, 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 history of drug or alcohol dependence within the last year, or prior prolonged history of dependence unless approved by the sponsor;
4. Are females of childbearing potential who are not surgically sterile, not refraining from sexual activity or not using reliable methods of contraception. Females of childbearing potential must not be pregnant (negative serum at the time of screening and negative serum or urine β-HCG on imaging day) or breastfeeding at screening. Females must agree to avoid becoming pregnant, and agree to refrain from sexual activity or to use reliable contraceptive methods for 24 hours following 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 a history of relevant severe drug allergy or hypersensitivity (Relevant severe drug allergies should be determined by the PI, and any questions about a subject's eligibility can be directed to Avid. If a subject has a history of severe drug allergies, it may be dangerous for them to participate in a study);
6. Are patients who have received an investigational medication under an FDA IND protocol within 30 days prior to the planned imaging session for this study, with the exception of medications allowed in the companion study and approval from sponsor. Additionally, the time between the last dose of the

previous experimental medication and imaging must be at least equal to 5 times the terminal half-life of the previous experimental medication.

7. Are patients who have received a radiopharmaceutical for imaging or therapy within the past 24 hours prior to either imaging session for this study.
8. Have evidence of amyloid deposition as demonstrated by a positive florbetapir F 18 PET scan.
9. Are patients who, 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 electronic Case Report Form (eCRF).

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 eCRF. 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, 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. PRODUCT RISK ASSESSMENT

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

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

There are no data on the effects of ^{18}F-AV-1451 Injection in human perinatal development. . For this reason, females must avoid becoming pregnant. Females 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)

The study will consist of the following sequence of activities:

7.1.1. Screening Visit: Visit 1

Screening may take place over several days. All screening assessments will preferably be performed within 60 days prior to the ^{18}F-AV-1451 PET imaging session.

Screening assessments will include**:**

- Informed consent;
- Demographics (age, gender, education, race, ethnicity);
- Medical history, concomitant medications;

- Disease history (date/months since symptom onset, date/months since diagnosis, family history of relevant neurologic disease);
- An ECG will be performed to assess the subject's cardiac status. If an ECG was performed within the last 12 months and is available for review, the ECG does not need to be repeated;
- Cognitive status interview, including MMSE;
- MRI of the brain, only for those subjects who do not have a prior MRI (obtained within one year of enrollment) available for submission to Avid and are able to tolerate one;
- Serum pregnancy test (women of childbearing potential);
- A physician will see the patient during the screening visit.
- Florbetapir F 18 PET scan (see section 7.1.1.1 for details)

7.1.1.1. Screening Florbetapir F 18 PET scan

The screening florbetapir F 18 PET scan is to be performed to assess for evidence of amyloid pathology and should be interpreted by the local reader prior to enrollment. Amyloid scans that have been obtained within 3 years of screening can be submitted for review by the local reader for enrollment criteria. If deemed interpretable, the subject would not need to complete the screening florbetapir F 18 PET scan.

- For women of childbearing potential, a negative pregnancy test must be obtained within 24 hours prior to injection; If screening serum pregnancy test obtained within 24 hours prior to injection, the pregnancy test need not be repeated.
- Height and body weight will be measured prior to injection.
- A physician or licensed/credentialed medical professional (that is, a PET technologist, imaging center nurse, or a regional equivalent) designated by the site principal investigator must see the subject prior to administration of Florbetapir F 18 Injection to determine if they are still suitable to undergo the scan;
- Vital signs will be taken (pulse rate, respiratory rate, supine blood pressure) immediately prior to injection of florbetapir F 18;
- Subjects will receive a single IV bolus injection of approximately 370 MBq (10 mCi) +10% of florbetapir F 18 followed by a saline flush. A 20-minute continuous, dynamic PET brain scan will begin approximately 50 minutes following the dose administration;
- A physician or licensed/credentialed medical professional (that is, a PET technologist, imaging center nurse, or a regional equivalent) designated by

the site principal investigator will see the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge;

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

7.1.2. ^{18}F-AV-1451 PET Imaging Visit: Visit 2

The ^{18}F-AV-1451 PET scan should be performed at least 16 hours apart from the Florbetapir F 18 PET scan due to the half-life of fluorine 18. The following assessments will be performed for all subjects:

- Females of childbearing potential will have a urine or serum pregnancy test prior to injection (the result must be negative for the subject to be administered ^{18}F-AV-1451);
- A physician or licensed/credentialed medical professional (that is, a PET technologist, imaging center nurse, or a regional equivalent) designated by the site principal investigator must see the subject prior to administration of ^{18}F-AV-1451 to determine if they are still suitable to undergo the scan;
- Vital signs will be taken in a supine position immediately prior to administration of ^{18}F-AV-1451 (within 30 minutes prior to injection) and at the completion of imaging at discharge.
- Body weight will be measured prior to injection.
- Subjects will receive a single IV bolus injection of approximately 370 MBq (10 mCi) ^{18}F-AV-1451 followed by a saline flush. A 30 minute dynamic image will begin approximately 75 minutes following the dose administration;
- Subjects will be observed continuously for signs of adverse events, or serious adverse events;
- A physician or licensed/credentialed medical professional (that is, a PET technologist, imaging center nurse, or a regional equivalent) designated by the site principal investigator will see the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge;
- A follow-up phone call to the subject, or designated decision maker, will be conducted 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.

7.2. Observations and Measurements

Informed Consent

Potential subjects will be allowed to read a written informed consent form. The principal investigator, or designee, will explain all study procedures, risks, and alternative therapies to 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.

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

Medical History

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

- Relevant demographic information
- Review of body systems
- Social history
- Medical and surgical history
- Concurrent medications

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

Vital Signs

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

- Screening Florbetapir F 18 Imaging
  - Immediately prior to injection of florbetapir F 18
- ^{18}F-AV-1451 Imaging Visit
  - Prior to the administration of ^{18}F-AV-1451 Injection
  - After the completion of imaging, prior to discharge.

Height and Weight

At both imaging visits body weight will be measured, lightly clothed. Height will only be measured as part of the ^{18}F-AV-1451 imaging visit.

Electrocardiogram

A resting ECG will be recorded at screening if a previous ECG performed within the last 12 months is not available for review.

Pregnancy Testing

- Serum beta hCG, qualitative: performed at screening for females of childbearing potential who are not surgically sterile. A serum pregnancy test may also be obtained prior to injection at the imaging visit if required by the local site.
- Urine beta hCG: performed at the ^{18}F-AV-1451 imaging visit and florbetapir F 18 imaging visit (except as specified in section 7.1.1.1) prior to injection for females of childbearing potential (defined as pre-menopausal, less than 2 years post-menopausal or not surgically sterile).

MRI

Electronic copies of volumetric brain MRI scans obtained as part of the site's companion protocol will be submitted to Avid, or designated imaging core lab. If one is not available for submission to Avid or designated imaging core lab, an MRI may be performed under this protocol if the subject is able to tolerate one. The MRI sequences and acquisition parameters will be described in a separate document.

Mini-Mental State Examination (MMSE)

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

Physician Visit

A physician must see the subject at screening to confirm that the subject is appropriate for participation in the trial. A physician or licensed/credentialed medical professional (that is, a PET technologist, imaging center nurse, or a regional equivalent) designated by the site principal investigator must see the subject at baseline, prior to drug administration and at study end, prior to discharge from the imaging sessions. At discharge, the physician or designee 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 and florbetapir F 18 image acquisition parameters and transmission procedures prior to site initiation.

7.4. Good Clinical Practice and Monitoring

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

This includes:

1. IRB approval: An investigation will be initiated at a study site only after the IRB for that study site has given their written approval of the protocol and informed consent;
2. Informed Consent: Study procedures will not be initiated until the informed consent form is signed;
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 FTD 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, consistent with the requirements of the State where the subject resides and local IRB guidance. Subjects with the capacity to understand that they are engaging in a research study should affirm that they do not object to participating by signing on the Subject Assent line of the consent form. Subjects

lacking the capacity to assent and/or dissent will not be precluded from participation, but would not be required to sign the consent form.

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

7.6. Documentation

^{18}F-AV-1451 and florbetapir F 18 PET scans will be saved in an appropriate electronic format as specified in the imaging manuals. A copy of all scans, including the MRI scans will be saved at the site/imaging center and a copy of each will be forwarded to the sponsor or to the designated imaging core lab as described in the imaging manuals. All other data required by the protocol will be recorded in the 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 its designees. Completed source documents and eCRFs may need to be made available and complete for an audit by the FDA, other international regulatory authorities, or Avid at any time. eCRFs and all other records must be filed in accordance with applicable laws and regulations (see Section 10.6).

7.7. Adverse Events (AE)

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

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

Additionally, any clinically significant findings from laboratory evaluations, vital sign measurements, or other study procedures including those that result in a diagnosis should be reported as an AE to Avid, or its designee**.**

7.7.1. Adverse Event Monitoring

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

7.7.2. Adverse Event Definitions

Adverse Events

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

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

Pre-existing conditions (i.e., undesirable experiences, signs or symptoms that begin prior to the Screening Visit) will be recorded on the medical history eCRF pages. During the study, site personnel will record any change in the condition(s) and occurrence and nature of any AEs. Signs and symptoms that are believed to be due to the pre-existing condition(s) (started prior to dose of study medication) do not have to be recorded in the AEs section of the eCRF, unless there is an increasing in frequency and severity. Additionally, signs or symptoms or changes in pre-existing conditions that occur outside the trial defined adverse event reporting period (e.g., between each imaging visit 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. Untoward medical occurrences will be considered associated with the use of Florbetapir F 18 injection, if they occur within 48 hours after Florbetapir F 18 injection administration. Adverse events associated with the use of ^{18}F-AV-1451 or Florbetapir F 18 injection will be recorded as treatment emergent relative to the respective drug. Adverse experiences that occur after administration of either drug but outside the 48 hour reporting window will not be reported unless the investigator believes they are attributable to the drug.

Trial-emergent adverse events are undesirable experiences, signs or symptoms that begin, or worsen in intensity or frequency, after the informed consent, and

prior to administration of study drug at the imaging visit. In order to capture possible adverse effects of trial participation, trial-emergent AEs will also be reported during the baseline imaging period but not during the 48 hour windows following the administration of ^{18}F-AV-1451 or Florbetapir. These will be recorded on the adverse event pages.

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

Serious Adverse Event (SAE)

A SAE is an AE that results in one of the following outcomes or constitutes one of the following events:

- Death;
- Initial or prolonged inpatient hospitalization (other than that required by protocol; "social hospitalization" or any hospitalization for non-medical reasons does not constitute a SAE);
- A life-threatening experience (that is, immediate risk of dying);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect;
- Considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Adverse Event

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

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, in order to determine the intensity (severity) of the event.

The following classifications should be used:

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

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

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

7.7.3. Adverse Event Documentation

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

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

7.7.4. Reporting of Serious Adverse Events

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

Serious adverse events occurring after a subject receives a dose of study drug will be collected in the eCRF as Adverse Events until 48 hours after the dosing of the study drug, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported in the eCRF as Adverse

Events unless the investigator feels the events were related to either investigational product or drug delivery system, or a protocol procedure If the investigator does not feel the event was related to the investigational product or drug delivery system or protocol procedure, then the event should be recorded in the eCRF as Medical History for the subject. Regardless of the investigator's assessment of relatedness or timing, all SAEs that occur after the subject receives the investigational product should be submitted to Lilly GPS for processing to determine applicability of any expedited reporting requirements..

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

8. STATISTICAL ANALYSIS

8.1. General Statistical Considerations

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

The study data collected under companion protocol such as but not limited to subjects' demographic and baseline characteristics, history taking, neurological and behavioral evaluations, and MRI will be transferred to Avid for analysis purposes. Amyloid scans used for review of enrollment criteria will also be transferred to Avid if applicable.

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 eCRFs as well as any derived variables will be presented.

8.1.1. Sample Size Estimation

This study will enroll up to 25 subjects. This sample size was chosen in order to allow for qualitative and descriptive review of ^{18}F-AV-1451 PET binding in subjects with clinically defined FTD. Based on prior studies, 10-15 cases are typically

sufficient for preliminary exploratory analysis. The sample size for this study is slightly larger to accommodate the heterogeneous pathology that underlies FTD. Results of the exploratory analysis from this study will permit planning of subsequent, hypothesis-driven studies.

8.1.2. Populations for Analysis

The efficacy population will include all patients for whom image data are available. All analyses involving tau imaging outcomes will be based on the efficacy population. Safety population will include all patients that received at least one dose of ^{18}F-AV-1451 compound or Florbetapir F 18. Safety evaluation will be based on safety population.

8.2. Analyses

8.2.1. Efficacy Analyses

^{18}F-AV-1451 images will be evaluated both by qualitative visual analysis and by regional SUVr. Descriptive statistics will be applied to describe the distribution of tau deposition as measured by ^{18}F-AV-1451 across clinical diagnosis groups and by florbetapir PET quantitation. Mean, standard deviation, median, minimum, and maximum values will be provided for continuous variables and counts and percentages will be provided for categorical variables.

Details of analyses will be provided in statistical analysis plan (SAP).

8.2.2. Safety Analyses

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

9. USE OF DATA AND PUBLICATION

Avid adheres to the Pharmaceutical Research and Manufacturers of America (PhRMA) Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results. A complete copy of these principles is available from Avid and can also be found at the PhRMA website (http://www.phrma.org). Avid's 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 or international regulatory authorities) at any time.

10.1. Institutional Review Board (IRB)

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

10.2. Informed Consent

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

10.3. Protocol Adherence

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

10.4. Documents Necessary for Initiation of the Trial

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

- Original signed and dated Statement of Agreement page;
- Copy of the IRB and radiation safety committee approval (if applicable);
- Copy of the IRB stamped approved consent form;
- Name and location of the laboratory utilized for laboratory assays, and other facilities conducting tests, including laboratory certification number and date of certification if available;
- List of reference range laboratory values; and
- Any additional licenses required in order to order to use ^{18}F-AV-1451 or Florbetapir F 18.

10.5. Study Drug Control

The receipt of clinical supplies (e.g. 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 Injections and Florbetapir F 18 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 and all drug supplies must be justified. 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 and Company 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 and Company must be notified immediately of any findings with the use of the drug that may suggest significant hazards, contraindications, adverse drug reactions (ADRs) and precautions pertinent to the safety of the drug. The investigator will be requested to complete a separate report form in addition to the information on the eCRF. See section 7.7.4 for reporting serious adverse events

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

10.8. Records Retention

All correspondence (e.g., with Avid, IRB, etc.) relating to this clinical trial should be kept in appropriate file folders. Records of subjects, source documents, and drug inventory sheets pertaining to the trial must be kept on file. Records must be retained until the date a marketing application (NDA) is approved for the drug for the indication for which it is being investigated, or until 2 years following the date of clinical trial termination or completion, whichever is later. If no application is

to be filed, or if the application is not approved for such indication, records should be kept until 2 years following the date of clinical trial termination or completion.

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

11. APPENDICES

11.1. References

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11.2. Trial Flow Chart

Evaluations	Screening Assessments [a]	Screening Florbetapir F 18 PET Scan[h]	^{18}F-AV- 1451 Imaging Visit
Signed Informed Consent	X		
Demographics	X		
Medical History	X		
Concomitant Medications	X		
ECG	X		
MMSE	X		
MRI	X[n]		
Serum beta-hCG Pregnancy Test	X[b]		
Urine Pregnancy Test		X[c]	X[c]
Vital Signs		X[d,]	X[d, ,f,]
PET Brain Scan		X[, g, h, i]	X[j, k,]
Evaluation by a physician	X	X[l]	X[l]
Adverse Events	X	X	X
Serious Adverse Events	X	X	X
Follow-up Phone Call[m]		X	X

a. Screening may take place over several days. All assessments must be performed prior to the ^{18}F-AV-1451 imaging session.
b. Serum beta-hCG pregnancy test at screening (for females of childbearing potential defined as pre-menopausal or less than 2 years post-menopausal and not surgically sterile).
c. For women of childbearing potential, a negative urine or serum (if required by local site) pregnancy test must be obtained within 24 hours prior to florbetapir F 18 injection and within 24 hours prior to 18F-AV-1451 injection.
d. Vital signs (pulse, respiratory rate, supine blood pressure) and weight will be taken prior to dose administration.
e. Height will be taken prior to dose administration
f. Vital signs (pulse, respiratory rate, supine blood pressure) will be taken after completion of the PET scan prior to discharge.
g. The screening florbetapir F 18 PET scan is to be performed to assess for evidence of amyloid pathology and should be interpreted by a local reader prior to enrollment

h. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of florbetapir F 18 Injection followed by a saline flush.
i. At approximately 50 minutes following florbetapir F18 injection, a continuous 20-minutes brain scan will begin
j. 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.
k. At approximately 75 minutes following ^{18}F-AV-1451 injection, a continuous 30-minute brain scan will begin.
l. A physician (or licensed/credentialed medical professional) must see the subject prior to drug administration and at study end, prior to discharge from the imaging session.
m. A follow-up phone call to the subject, or designated decision maker, will be conducted within 2 or 3 business days of each 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.
n. If a prior MRI is not available for submission to Avid or designated imaging core lab, an MRI may be performed under this protocol if the subject is able to tolerate one.

INVESTIGATOR'S AGREEMENT TO PROTOCOL

Protocol ^{18}F-AV-1451-A19: ^{18}F-AV-1451 PET Imaging in Subjects with Frontotemporal Dementia

Date and Version: 05 MAY 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