Protocol Number: ^{18}F-AV-1451-A11

^{18}F-AV-1451 PET Imaging in Professional Fighters

Date and Version:
13 July 2015, Amendment 1

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

Sponsor:
Avid Radiopharmaceuticals
Philadelphia, Pennsylvania USA

Approvals/Signatures and Date:

[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-A11

"^{18}F-AV-1451 PET Imaging in Professional Fighters"

Planned number of subjects (Enrolled): Approximately 30

This study will be divided into the following groups:

1. Approximately 15 active professional fighters (boxers and mixed martial artists) who have had at minimum 10 professional fights.
    a. Approximately 10 with cognitive impairment
    b. Approximately 5 without cognitive or behavioral complaints
2. Approximately 15 retired professional fighters (boxers and mixed martial artists).
    a. Approximately 10 with cognitive impairment
    b. Approximately 5 without cognitive or behavioral complaints

Subjects will be recruited from the pool of participants in the Professional Fighters Brain Health Study (PFBHS).

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: 1-3 centers in the United States

Trial Objectives:

The primary objectives of this study are:

- To explore the use of ^{18}F-AV-1451 as a biomarker for brain injury related to repetitive head trauma; and
- To examine the relationship between clinical presentation and tau deposition as measured by ^{18}F-AV-1451 uptake in active and retired professional fighters.

A secondary objective of this study is:

- To expand the ^{18}F-AV-1451 safety database.

Eligibility:

Only subjects duly consented and enrolled in the PFBHS protocol (conducted by the Cleveland Clinic with Dr. Charles Bernick as Principal Investigator) will be considered for participation in this study (see Section 5.3, Selection of Subjects).

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

Study Design:

This is a phase I study that will evaluate imaging characteristics of ^{18}F-AV-1451 in active and retired professional fighters enrolled in the PFBH study.

Subjects enrolled in the PFBH study will be contacted to participate and must provide informed consent before starting any ^{18}F-AV-1451-A11 study procedures. In addition to consenting to study procedures, participants will consent to have Magnetic Resonance Imaging (MRI) images/data, including volumetric, functional and standard clinical sequences, and cognitive/behavioral data as part of the PFBHS made available to this study to allow for analysis and comparison. Screening assessments may take place over several days, within 90 days of the ^{18}F-AV-1451 Positron Emission Tomography (PET) scan, and will include demographic information, cognitive testing and safety assessments. Subjects may be permitted to return for the ^{18}F-AV-1451 PET scan after the 90 day window with sponsor approval if the investigator does not recognize any significant medical changes. If a volumetric MRI has not been performed as part of PFBHS within six months of the ^{18}F-AV-1451 PET imaging visit, a volumetric MRI is to be performed as part of this study's screening assessments.

Subjects who qualify for the study will return to the clinic at a later date for the ^{18}F-AV-1451 PET imaging visit. For the ^{18}F-AV-1451 PET imaging visit, an intravenous catheter will be placed for IV administration of ^{18}F-AV-1451 Injection. Subjects will receive a single IV bolus injection with a target dose of 370 MBq (10 mCi) of ^{18}F-AV-1451 Injection followed by a saline flush. At approximately 75 minutes following injection, a continuous 30-minute brain scan will begin. Adverse events will be monitored continuously during the imaging session. A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to injection and prior to discharge from the imaging center. If a designee performs this activity, a physician must be available to provide medical consultation.

All professional fighters $\geq$ 50 years of age and other participants in whom, and in the opinion of the investigator, the clinical presentation suggests a possible diagnosis of Alzheimer's disease (AD) will return to the clinic for a florbetapir F 18 PET imaging visit. The PET imaging visits must be performed no more than 60 days apart. For the florbetapir F 18 PET imaging visit, an intravenous catheter will be placed for IV administration of Florbetapir F 18 Injection. 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. At approximately 50 minutes following injection, a continuous 10-minute brain scan will begin. Adverse events will be monitored continuously during the imaging session. A physician, or physician designee, must evaluate the subject for adverse events prior to injection and prior to discharge from the imaging center.

A follow-up phone call to the subject, or informant where applicable, will be conducted between 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.

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

Analyses will explore the relationship among ^{18}F-AV-1451 uptake measurements, florbetapir SUVR (where applicable), cognitive and neuropsychiatric measurements, and other collected biomarkers in subjects, and will explore if the ^{18}F-AV-1451 uptake measurements are different across patient enrollment groups.

Assessments and Endpoints:

All subjects will have a screening visit, a ^{18}F-AV-1451 PET imaging visit, and a follow-up phone call after the imaging visit. All professional fighters $\geq$ 50 years of age and other participants in whom, and in the opinion of the investigator, the clinical presentation suggests a possible diagnosis of AD will also have a florbetapir F 18 PET imaging visit and a follow-up phone call after the imaging visit.

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

Statistical Methods:

Descriptive Statistics will be applied to describe the ^{18}F-AV-1451 uptake and florbetapir SUVR distribution by subject enrollment groups (active/retired professional fighters and cognitive impaired/normal). ANOVA test, or comparable non-parametric tests such as Kruskall-Wallis test when ANOVA's pre-requisites are not met, will be conducted to detect the differences in ^{18}F-AV-1451 uptake measurements across the enrollment groups. If an overall difference is detected, then a two sample t-test, or Wilcoxon rank sum test when the pre-requisite of t-test is not met, will be applied to test if there are differences seen in ^{18}F-AV-1451 uptake measurements between pair-wised enrollment groups. Additional exploratory analyses will be applied to explore the relationship among ^{18}F-AV-1451 uptake measurements, cognitive and neurological measurements, and other collected biomarkers in the study subjects.

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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
ANOVA	A collection of statistical models used to analyze the differences between group means and their associated procedures
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
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.
CTE	Chronic Traumatic Encephalopathy
ECG	Electrocardiogram
EDTA	(ethylenediaminetetraacetic acid) is the most commonly used anticoagulant in evacuated tubes
Efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.
	End of Synthesis

EOS	
FDA	US Food and Drug Administration
FDG	^{18}F - Fluorodeoxyglucose
GCP	Good Clinical Practice
hERG	human Ether-à-go-go-Related Gene
IB	Investigator's Brochure
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
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
PFBHS	Professional Fighters Brain Health Study
pH	a measure of the acidity or basicity of an aqueous solution
PHF tau	Paired Helical Filament tau
PhRMA	Pharmaceutical Research and Manufacturers of America
v/v	Percentage solution
QT	A measure of the time between the start of the Q wave and the end of the T wave
QTcF	Fredericia's repolarization correction formula of the QT interval
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.
SOP	Standard Operating Procedure
SUVR	Standard Uptake Value Ratio
SOC	System Organ Class
TBI	Traumatic Brain Injury
TdP	Torsades de Pointes

1. INTRODUCTION

Traumatic brain injury (TBI) is a major public health concern with 1.7 million people in the United States suffering a TBI each year (Faul et al., 2010). There is longstanding evidence linking a history of TBI to increased risk for Alzheimer's disease (AD) (Graves et al., 1990), and emerging concern that a single TBI could initiate long-term processes leading to dementia that is independent of AD (Johnson et al., 2010). Pathologically, amyloid-beta (Aβ) deposits have been identified following a single TBI in approximately 30% of patients (Huber et al., 1993; Ikonomovic et al., 2004). Plaques found acutely following TBI are typically diffuse, in contrast to the thioflavine-S-positive neuritic plaques characteristic of AD. Thus far, neurofibrillary tangles (NFTs) have not been identified following a single TBI in humans; although the neuropathological evidence is sparse, with the only study examining this issue limited to patients dying within 4 weeks of injury (Smith et al., 2003).

Emerging research suggests that tau pathology similar to that seen in Alzheimer's disease may be more likely after even a single TBI episode (Johnson et. al, 2012). Chronic repetitive TBI has been linked to the pathological entity known as chronic traumatic encephalopathy (CTE). CTE is a clinic-pathological entity characterized post mortem by tau pathology that has been linked to individuals exposed to repetitive, often mild or concussive, head injury such as boxers (Corsellis et al., 1973; Dale et al. 1991; Geddes et al., 1999) and professional football players (McKee et al., 2009; McKee et al., 2013).

The Professional Fighters Brain Health Study (PFBHS) being conducted at the Cleveland Clinic Lou Ruvo Center for Brain Health is a longitudinal study that focuses on a sample of active and retired professional fighters, and compares them with a control cohort matched for age and level of education. The primary objective of the PFBHS is to determine the relationship between measures of head trauma exposure and other potential modifiers and changes in brain imaging, neurological and behavioral function over time (Bernick, 2013). In this context, the addition of an imaging biomarker that could identify the presence of underlying tau pathology might be useful in understanding the etiology and evolution of CTE, and could potentially identify cases at risk for subsequent neurodegeneration or other clinically important outcomes with implications for management of CTE and/or TBI cases.

^{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 from brains of AD patients yielded a K_d value of 0.54 nM.

AV-1451 was assessed in competitive binding assays against a panel of 72 of the most common central nervous system (CNS) targets and no clinically relevant inhibition was seen. AV-1451 was positive in the i*n vitro* hERG assay; however, *in vivo* cardiovascular safety pharmacology assessments in dogs showed no evidence of QT prolongation at doses up to 50x the intended maximum human dose (MHD). Nonetheless, until sufficient human cardiovascular safety data are available, initial clinical studies will exclude subjects with a history of risk factors for Torsades de Pointes and subjects taking drugs known to prolong the QT interval.

In vivo safety pharmacology studies were also conducted in rats to determine potential effects on the CNS and respiratory systems. In these studies no clinically relevant effects were reported at doses exceeding 100x the intended MHD. Additionally, non-radioactive AV-1451 has been tested in single and repeat dose toxicology studies in rat and dog. In each of these studies the no observable adverse effect levels (NOAELs) were the highest doses tested (150x MHD for single, 50x MHD for repeat).

Potential genotoxicity of non-radioactive AV-1451 was tested in both *in vitro* and *in vivo* assays. In the *in vitro* assays, AV-1451 tested positive for potential genotoxicity. However, in the *in vivo* rat micronucleus assay at doses up to 750x MHD (scaled allometrically), AV-1451 showed no evidence of genotoxicity. The different results in the *in vitro* genotoxicity assays and the *in vivo* micronucleus study are likely related to differences in the exposure conditions encountered by the target cells in the different test systems. *In vivo*, AV-1451 is cleared rapidly; however, the *in vitro* experiments employ static, prolonged exposure of cells to high concentrations of the test article. While the *in vitro* data show the potential for genotoxicity, the *in vivo* data provide assurance that genotoxicity is unlikely to occur at clinically-relevant doses for human diagnostic studies.

Human dosimetry has been obtained in nine subjects. Generally, the radiotracer distribution was consistent among the subjects and showed rapid hepatobiliary clearance. There were three organs that received estimated doses higher than 0.05 mSv/MBq. The organ that received the largest estimated dose was the upper large intestinal wall (0.0962 ± 0.0134 mSv/MBq), followed by the small intestine and the liver. The Effective Dose was 0.0241 ± 0.0016 mSv/MBq. This results in an estimated Effective Dose of 8.92 mSv for an anticipated 370 MBq (10 mCi) injection and is comparable to the effective dose of approved ^{18}F-labeled compounds such as fluorodeoxyglucose (FDG) and florbetapir F 18 injection.

^{18}F-AV-1451 may be useful as a marker of tau pathology in patients with AD and other neurodegenerative disorders (Figures 1 and 2). Several preliminary studies using ^{18}F-AV-1451 have been completed (e.g., Chien et al., 2013). Based on this rationale, the goal of this protocol is to perform ^{18}F-AV-1451 PET imaging on active and retired professional fighters enrolled in the PFBHS protocol and explore its potential as a biomarker for brain injury related to repetitive head trauma.

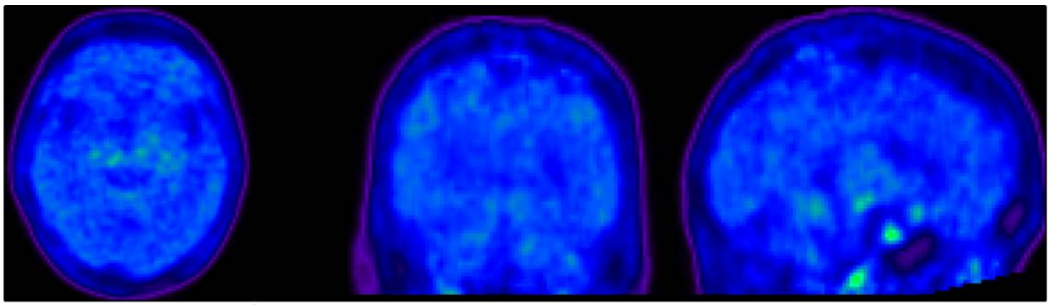


Figure 1: [redacted] female control subject (MMSE = 29)

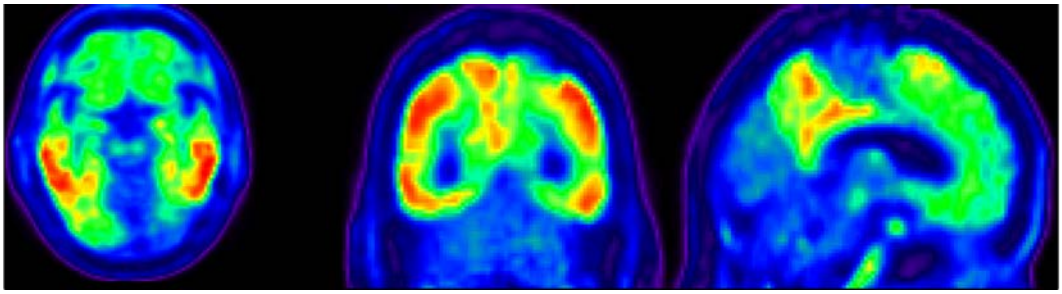


Figure 2: [redacted]l male AD subject (MMSE = 18)

2. TRIAL OBJECTIVES

The primary objectives of this study are:

- To explore the use of ^{18}F-AV-1451 as a biomarker for brain injury related to repetitive head trauma; and
- To examine the relationship between clinical presentation and tau deposition as measured by ^{18}F-AV-1451 uptake in active and retired professional fighters.

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]

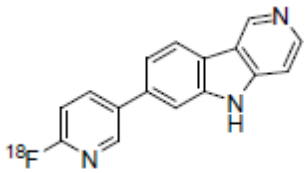
[redacted]

1-3 centers in the United States will participate in this trial.

4. TEST DRUG AND CONTROL AGENTS

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

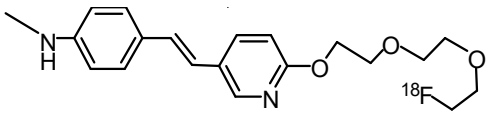
7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole



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 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.

4.6 Formulation and Dose ^{18}F-AV-1451 Injection

^{18}F-AV-1451 Injection is a clear solution containing ^{18}F-AV-1451 (drug substance) formulated for intravenous bolus administration. Depending on the manufacturer, ^{18}F-AV-1451 Injection will be formulated in:

- aqueous 21 mM sodium phosphate solution containing up to 10% (v/v) ethanol, or
- a solution containing 10% (v/v) ethanol, USP in 0.9% sodium chloride injection, USP.

Drug product of either formulation is manufactured to meet one common set of specifications.

The expiration time and date of ^{18}F-AV-1451 Injection are provided on the outer label of each dose based on specific activity or strength. ^{18}F-AV-1451 Injection should be stored at room temperature.

4.7 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.

4.8 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.

4.9 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.

4.10 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 active and retired professional fighters enrolled in the PFBH study.

Subjects enrolled in the PFBH study will be contacted to participate and must provide informed consent before starting any ^{18}F-AV-1451-A11 study procedures. In addition to consenting to study procedures, participants will consent to have Magnetic Resonance Imaging (MRI) images/data, including volumetric, functional and standard clinical sequences, and cognitive/behavioral data as part of the PFBHS made available to this study to allow for analysis and comparison. Screening assessments may take place over several days, within 90 days of the ^{18}F-AV-1451 PET scan, and will include demographic information, cognitive testing and safety assessments. Subjects may be permitted to return for the ^{18}F-AV-1451 PET scan after the 90 day window with sponsor approval if the investigator does not recognize any significant medical changes. If a volumetric MRI has not been performed as part of PFBHS within six months of the ^{18}F-AV-1451 PET imaging visit, a volumetric MRI is to be performed as part of this study's screening assessments.

Subjects who qualify for the study will return to the clinic at a later date for the ^{18}F-AV-1451 PET imaging visit. For the ^{18}F-AV-1451 PET imaging visit, an intravenous catheter will be placed for IV administration of ^{18}F-AV-1451 Injection. Subjects will receive a single IV bolus injection with a target dose of 370 MBq (10 mCi) of ^{18}F-AV-1451 Injection followed by a saline flush. At approximately 75 minutes following injection, a continuous 30-minute brain scan will begin. Adverse events will be monitored continuously during the imaging session. A physician or a licensed/credentialed medical professional (i.e. a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to injection and prior to discharge from the imaging center. If a designee performs this activity, a physician must be available to provide medical consultation.

All professional fighters $\geq$ 50 years of age and other participants in whom, and in the opinion of the investigator, the clinical presentation suggests a possible diagnosis of AD will return to the clinic for a florbetapir F 18 PET imaging visit. The PET imaging visits must be performed no more than 60 days apart. For the florbetapir F 18 PET imaging visit, an intravenous catheter will be placed for IV administration of Florbetapir F 18 Injection. 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. At approximately 50 minutes following injection, a continuous 10-minute brain scan will begin. Adverse events will be monitored continuously during the imaging session. A physician, or physician designee, must evaluate the subject for adverse events prior to injection and prior to discharge from the imaging center.

A follow-up phone call to the subject, or informant where applicable, will be conducted between 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.

Analyses will explore the relationship among ^{18}F-AV-1451 uptake measurements, florbetapir SUVR (where applicable), cognitive and neuropsychiatric measurements, and other collected biomarkers in subjects, and will explore if the ^{18}F-AV-1451 uptake measurements are different across patient enrollment groups.

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 of approximately 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 (10 mCi) with a maximum human dose (MHD) limited to 20 μg of compound by weight. This dose is 150 fold lower than the NOAEL observed in the rat single dose toxicity study and is 50 fold lower than the NOAEL observed in the rat and dog repeat dose toxicity studies.

Human dosimetry has been obtained in nine subjects. The results estimated an Effective Dose of 8.92 mSv for an anticipated 370 MBq (10 mCi) injection and is comparable to the effective dose of approved ^{18}F-labeled compounds such as FDG and florbetapir F 18 injection.

The proposed dose has been shown to have acceptable image quality in previous human studies. No treatment related adverse events have been reported using this regimen.

5.3 Selection of Subjects

5.3.1 Inclusion Criteria

All subjects must meet all of the following criteria to enroll in this trial:

1. Males that have consented, are currently enrolled in the PFBHS protocol, and have participated in a minimum of 10 professional fights;
2. Can tolerate PET scan procedures; and
3. Have the ability to provide informed consent for study procedures (if the patient is ineligible to give informed consent, based on local standards, the patient's legal representative may consent on behalf of the patient, but the patient must still confirm assent).

Subjects with cognitive impairment should meet the following criteria:

1. Have subjective cognitive complaints or objective decline or impairment as determined by the investigator.

5.3.2 Exclusion Criteria

Subjects will be excluded from enrollment if they:

1. Have behavior dysfunction that is likely to interfere with imaging. The investigator should carefully consider whether subjects with behavior dysfunction will be able to complete the imaging session(s) and may be enrolled only after discussion and with approval of the sponsor;

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

3. Have current clinically significant cardiovascular disease, or clinically significant abnormalities on screening ECG (including but not limited to QTcF>450 msec. Subjects with QTcF>450 msec in the presence of bundle branch block may be enrolled after discussion with sponsor);

4. 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);

5. Have a current clinically significant infectious disease, endocrine or metabolic disease, pulmonary, renal or hepatic impairment, or cancer that the investigator believes would affect study participation or scan results;

6. Have had a non-study related radiopharmaceutical imaging or treatment procedure within 7 days prior to the ^{18}F-AV-1451 imaging session;

7. Have current drug or alcohol dependence or alcohol dependence within the past 2 years; and

8. 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. WARNINGS/PRECAUTIONS

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

In brief, ^{18}F-AV-1451 Injection is an experimental imaging agent that will be used at relatively low (tracer) doses. Because ^{18}F-AV-1451 Injection is under clinical investigation, it is recommended that subjects receiving ^{18}F-AV-1451 Injection be followed closely by means of adverse event reporting.

There are no data on the effects of ^{18}F-AV-1451 Injection in human perinatal development. For this reason, males enrolled in this study must agree to use adequate contraceptive methods, if they engage in sexual activity for at least 90 days after 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:

Subjects currently enrolled in the PFBH study protocol will be contacted to participate. Screening assessments may take place over several days, within 90 days of the ^{18}F-AV-1451 PET scan, and will include:

- Informed Consent will take place before any ^{18}F-AV-1451-A11 study procedures;
- Demographics (birth year, gender, race, ethnicity, education, alcohol, drug use and smoking);
- Medical history and concomitant medications;
- Safety assessments: Vital signs (pulse rate, respiratory rate, supine blood pressure, height and weight), ECG (with results reviewed prior to ^{18}F-AV-1451 administration), and safety labs (hematology, chemistry and urinalysis) including plasma thiamine (vitamin B1) level;
- Mini-Mental State Examination (MMSE);
- Digit span forward and backward;
- Beck Depression Inventory II;
- If a volumetric MRI has not been performed as part of PFBHS within six months of the ^{18}F-AV-1451 PET imaging visit, a volumetric MRI is to be performed as part of this study's screening assessments; and
- A physician will see the subject during the screening assessments.

7.1.2 Imaging Visit(s)

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

- A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to administration of ^{18}F-AV-1451 Injection to determine if they are still suitable to undergo the scan. If a designee performs this activity, a physician must be available to provide medical consultation;
- Vital signs will be taken (pulse rate, respiratory rate, supine blood pressure) at the following time points:
  - Prior to administration of ^{18}F-AV-1451 Injection (Weight will also be collected)
  - Within 5 minutes after completion of injection of ^{18}F- AV-1451 Injection
  - After completion of the PET scan prior to discharge;
- Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of ^{18}F-AV-1451 Injection followed by a saline flush.
- At approximately 75 minutes following injection, a continuous 30-minute brain scan 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 or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge. If a designee performs this activity, a physician must be available to provide medical consultation; and
- A follow-up phone call to the subject, or informant where applicable, 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.

Florbetapir F 18 PET Imaging Session

All professional fighters ≥ 50 years of age and other participants in whom, and in the opinion of the investigator, the clinical presentation suggests a possible diagnosis of AD will return to the clinic for a florbetapir F 18 PET imaging visit. The PET imaging visits must be performed no more than 60 days apart.

- A physician, or physician designee, 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 and weight) immediately prior to injection of florbetapir F 18;
- Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of florbetapir F 18 followed by a saline flush;
- At approximately 50 minutes following injection, a continuous 10-minute brain scan will begin;
- Adverse events will be continuously monitored during the Florbetapir F 18 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, or physician designee, 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 informant where applicable, 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, including medical care for head trauma
- 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 as part of the screening visit and at the following time points:

- Florbetapir F18 Imaging Visit
  - Prior to injection of florbetapir F 18
- ^{18}F-AV-1451 Imaging Visit
  - Prior to the administration of ^{18}F-AV-1451 Injection
  - Within 5 minutes after completion of injection of ^{18}F-AV-1451 Injection
  - After the completion of imaging, prior to discharge.

Height and Weight

At both the screening visit and imaging visit (prior to ^{18}F-AV-1451 and florbetapir F 18 administration) body weight will be measured, lightly clothed. Height will only be measured as part of the screening visit.

Electrocardiogram (ECG)

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

Volumetric MRI

If a volumetric MRI has not been performed as part of PFBHS within six months days of the ^{18}F-AV-1451 PET imaging visit, a volumetric MRI is to be performed as part of this study's screening assessments. The specific parameters for the MRI will be described in a separate document.

Clinical Laboratory Tests

Clinical laboratory evaluation will be performed at the site's local laboratory as part of the screening visit.

Tests will include:

- **Hematology** (4 mL EDTA);
- **Chemistry** (8.5 mL blood);
- **Urinalysis** (10 mL, urine); and
- **Thiamine** (vitamin B1; 4.0 mL blood).

A list of analytes and reference range laboratory values will be provided by the site to Avid.

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. The MMSE will be assessed during the screening visit.

Digit span forward and backward (Wechsler Memory Scale-Revised (WMS-R))

Digit Span is composed of two tasks administered independently of each other: Digits Forward and Digits Backward. On both tasks, the examiner reads a series of number sequences to the subject. For each Digits Forward item, the subject is required to repeat the number sequence in the same order as presented. For Digits Backward, the subject is required to repeat the number sequence in the reverse order.

Beck Depression Inventory-II

The Beck Depression Inventory-II (Beck, Steer and Brown, 1996) is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression.

Physician Visit

A physician must see the subject during the screening visit. A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to administration of ^{18}F-AV-1451 Injection and prior to discharge from the imaging center. If a designee performs this activity, a physician must be available to provide medical consultation. A physician, or physician designee, must see the subject at baseline, prior to drug administration and at study end, prior to discharge from the florbetapir F 18 imaging session. At discharge, the physician or licensed/credentialed medical professional (or designee for the florbetapir F 18 imaging visit) 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 subject signs the informed consent form;
3. Recording and monitoring of adverse events as outlined in Section 7.7.3 including the notification of study site clinical investigators, local IRBs and the FDA regarding serious adverse event;
4. Avid RP's obligation to monitor the participating center on a regular basis; and
5. The termination of a center or the trial if conditions apply, as outlined in Section 5.6.

7.5 Informed Consent and Subject Information

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

All informed consent forms must be approved by Avid or designee, and by the appropriate Institutional Review Board (IRB). No study related procedures shall be performed prior to completion of the informed consent process, and signing of the consent form. A copy of the signed informed consent should be given to the patient 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 conducted per PFBH study protocol, will be saved at the site/imaging center and a copy of each will be forwarded to the sponsor 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. The 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 event resolution). 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 increase in frequency and severity.

Trial-emergent adverse events are undesirable experiences, signs or symptoms that begin, or worsen in intensity or frequency, after the informed consent, and prior to administration of the study drug at the imaging visit. Adverse events that occur between the florbetapir F 18 and the ^{18}F-AV-1451 PET scans outside the 48 hour windows will also be considered trial-emergent adverse events. These will be recorded on the adverse event eCRFs.

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

The end of study, for the purpose of adverse event reporting, is defined as 48 hours after the last study drug administration (^{18}F-AV-1451 or Florbetapir F 18 Injection).

Serious Adverse Event (SAE)

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

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

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

Unexpected Adverse Event

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

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

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

8. STATISTICAL ANALYSIS

8.1 General Statistical Considerations

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

The study data collected under PFBHS 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.

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.

Descriptive Statistics will be applied to describe the ^{18}F-AV-1451 uptake and florbetapir SUVR distribution by subject enrollment groups (active/retired professional fighters and cognitive impaired/normal). ANOVA test, or comparable non-parametric tests such as the Kruskall-Wallis test when ANOVA's pre-requisites are not met, will be conducted to detect the differences

in ^{18}F-AV-1451 uptake measurements across the enrollment groups. If an overall difference is detected, then a two sample t-test, or Wilcoxon rank sum test when the pre-requisite of t-test is not met, will be applied to test if there are differences seen in ^{18}F-AV-1451 uptake measurements between pair-wised enrollment groups. Additional exploratory analyses will be applied to explore the relationship among ^{18}F-AV-1451 uptake measurements, cognitive and neurological measurements, and other collected biomarkers in the study subjects.

Additional details concerning statistical analyses will be included in the Statistical Analysis Plan (SAP) to be completed per Avid SOP.

8.2 Safety Analysis

Vital sign measurements will be summarized by subject(s) and by evaluation time point(s). Changes from baseline (pre-dose time point) values will be determined and summarized.

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

Discontinuation

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

Vital Signs

Changes in vital signs from baseline will be summarized.

8.3 Image Analysis

All ^{18}F-AV-1451 PET images obtained starting at 75 minutes post injection will be analyzed. Additional details concerning image analyses will be included in a separate document to be completed prior to the end of the study.

Florbetapir F 18 images will be analyzed as previously published (Clark et al. 2011, 2012).

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. A multi-center publication, reporting the primary analysis data set, should precede any other publications.

10. INVESTIGATOR'S REGULATORY OBLIGATIONS

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

10.1 Institutional Review Board (IRB)

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

10.2 Informed Consent

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

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 and Florbetapir F 18 Injections 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 as specified in the imaging manual.

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

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

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

10.7 Adverse Events

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

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

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

10.8 Records Retention

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

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person who

will accept the responsibility. Notice of transfer must be made to and agreed upon by Avid.

11. APPENDICES

11.1 References

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11.2 Trial Flow Chart

Evaluations	Screening Assessments[a]	^{18}F-AV- 1451 Imaging Visit	End of ^{18}F-AV-1451 Imaging (prior to discharge)	Follow-up Phone Call[b]	Florbetapir F 18 Imaging Visit[c]	End of Florbetapir F 18 Imaging (prior to discharge)	Follow-up Phone Call[b]
Signed Informed Consent	X						
Demographics	X						
Medical History	X						
Concomitant Medications	X						
Vital Signs	X[d]	X[e, f]	X[g]		X[e]		
Clinical Lab Tests	X[h]						
ECG	X[i]						
MMSE, Beck Depression Inventory II, Digit span forward/backward	X						
MRI	X[j]						
PET Brain Scan		X[k, l]			X[m, n]		
Evaluation by a physician	X	X[o]	X[o]		X[p]	X[p]	
Adverse Events	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X

a. Screening may take place over several days. All assessments must be performed within 90 days prior to the ^{18}F-AV-1451 imaging session. Subjects may be permitted to return for the ^{18}F-AV-1451 PET scan after the 90 day window with sponsor approval if the investigator does not recognize any significant medical changes.
b. A follow-up phone call to the subject, or information where applicable, 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.
c. For all professional fighters $\geq$ 50 years of age and other participants in whom, and in the opinion of the investigator, the clinical presentation suggests a possible diagnosis of AD.
d. Screening vital signs include pulse rate, respiratory rate, supine blood pressure, height and weight.
e. Vital signs (pulse, respiratory rate, supine blood pressure) and weight will be taken prior to dose administration.
f. Vital signs (pulse, respiratory rate, supine blood pressure) will be taken within 5 minutes after completion of injection of dose administration.
g. Vital signs (pulse, respiratory rate, supine blood pressure) will be taken after completion of the PET scan prior to discharge.
h. Safety labs to include hematology, chemistry and urinalysis including plasma thiamine (vitamin B1) level.
i. ECG (with results reviewed prior to ^{18}F-AV-1451 administration).
j. If a volumetric MRI has not been performed as part of PFBHS within six monthsof the ^{18}F-AV-1451 PET imaging visit, a volumetric MRI is to be performed as part of this study's screening assessments.
k. 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.
l. At approximately 75 minutes following ^{18}F-AV-1451 injection, a continuous 30-minute brain scan will begin.
m. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of florbetapir F 18 followed by a saline flush.
n. At approximately 50 minutes following Florbetapir F 18 injection, a continuous 10-minute brain scan will begin.
o. Or a licensed/credentialed medical professional (i.e. PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator. If a designee performs this activity, the physician must be available to provide medical consultation.
p. Or physician designee.

INVESTIGATOR'S AGREEMENT TO PROTOCOL

Protocol ^{18}F-AV-1451-A11: "^{18}F-AV-1451 PET Imaging in Professional Fighters"

Date and Version: 16 June 2015, Amendment 1

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

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

_____ _____

Printed Name Date

_____

Signature