18F-AV-1451-A24 Protocol Amendment 1

A Multicenter Screening Study With Flortaucipir F 18 in Patients With Early Symptomatic AD

NCT03467477

Approval date: 17 Apr 2018

Protocol Number: ^{18}F-AV-1451-A24

A multicenter screening study with flortaucipir F 18 in patients with early symptomatic AD; #2.

Date and Version:

17 April 2018

Amendment #1

Name of Compound:

Flortaucipir F 18 (^{18}F-AV-1451)

Sponsor:

Avid Radiopharmaceuticals, Inc.

Philadelphia, Pennsylvania USA

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

Title of Study: ^{18}F-AV-1451-A24

A multicenter screening study with flortaucipir F 18 in patients with early symptomatic AD; #2

Planned number of subjects (Enrolled): Approximately 500

Name of compound: flortaucipir F 18 (^{18}F-AV-1451)

Dose: 370 MBq (10 mCi)

Route of Administration: Intravenous (IV) bolus

Study Phase: II

Study Centers: Approximately 10 centers in North America

Trial Objectives:

The primary objective of the protocol is:

- To pre-screen patients via a flortaucipir F 18 scan, who have objectively verified cognitive impairment and etiology diagnosed or suspected to be Alzheimer's disease (AD), and have indicated their interest in participating in Lilly sponsored trials that require tau imaging for inclusion.

The secondary objective of the protocol is:

- To expand the flortaucipir F 18 safety database.

Eligibility: See Section 5.3, Selection of Subjects.

Study Design:

Study ^{18}F-AV-1451-A24 is a multicenter screening study in patients with early symptomatic AD (defined as prodromal AD and mild dementia due to AD).

All patients will provide informed consent before starting any study procedures. This pre-screening study targets patients who are interested in participating in Lilly AD therapeutic clinical trials and have expressed a preliminary interest in a trial similar to the LMDC trial, and who are not known to meet any of the exclusion criteria for trials similar to LMDC based on medical history and clinical examination. However, consent for this protocol does not constitute consent for any Lilly AD therapeutic trial, and subjects who qualify for this protocol may still

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

fail to qualify for Lilly AD therapeutic trials based on the results of this protocol or based on additional testing performed in those subsequent trials.

Screening assessments will include demographic information, cognitive testing, disease history, concomitant medications, vital signs, ECG and medical history. Patients who are deemed eligible to continue will complete a flortaucipir F 18 PET scan.

Patients who meet eligibility criteria will participate in this protocol until they have completed their flortaucipir F 18 PET scan and safety follow-up call, or they discontinue, withdraw consent, or if the sponsor decides to end this protocol early.

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

The following will be completed during the screening visit:

- Informed consent for patient;
- Demographics (age, gender, years of education, race, ethnicity); weight/height
- Medical and surgical history, concomitant medications;
- Vital Signs (pulse, respiratory rate, supine blood pressure);
- An ECG will be performed to assess the participant's cardiac status. If an ECG was performed within the last 12 months of the flortaucipir (^{18}F) PET Imaging Visit and is available for review, the ECG does not need to be repeated.
- ApoE status, if available;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of relevant neurologic disease);
- Cognitive status interview, including:
  - Mini Mental State Examination (MMSE) to be performed using Serial-7's on all patients;
  - CogState Brief Battery (CBB) to be performed on all patients
- A physician will see the patient during the screening visit; and
- For women of childbearing potential, a negative serum pregnancy test must be obtained at the screening visit.

After screening, eligible patients will complete an imaging visit and safety follow-up call, refer to Section 7.1.2 for details

Sponsor:	**Name of Compound:**	**Active Ingredient(s):**
Avid Radiopharmaceuticals, Inc.	Flortaucipir F 18 (^{18}F-AV-1451)	7-(6-[F-18]fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole
Statistical Methods: Descriptive analyses will be applied to summarize patients' demographic and baseline characteristics, and qualitative and quantitative assessments of the flortaucipir F 18 PET image.		

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

Aβ	Beta amyloid
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADRs	Adverse Drug Reactions
Adverse Event (AE)	Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
CBB	CogState Brief Battery
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.
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FDG	^{18}F – Fluorodeoxyglucose
GCP	Good Clinical Practice
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational New Drug
Institutional Review Board /Independent Ethics Committee	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare and human rights of the subjects participating in a clinical study are protected.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator (PI).
IV	Intravenous
K_d	Dissociation Constant
keV	Kiloelectron volt
LAR	Legally Authorized Representative
MBq	Megabecquerel
mCi	Millicurie
MCI	Mild Cognitive Impairment
MHD	Maximum Human Dose
MMSE	Mini Mental Status Exam
MRI	Magnetic Resonance Imaging
mSv	Millisievert
NDA	New Drug Application
nM	Nanomolar
NOAEL	No Observable Adverse Effect Level

PET	Positron Emission Tomography
PhRMA	Pharmaceutical Research and Manufacturers of America
SAE	Serious Adverse Event
SOP	Standard Operating Procedures

1. INTRODUCTION

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

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

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

Flortaucipir F 18 (^{18}F-AV-1451) (originally named [F-18]T807 by Siemens Molecular Imaging Biomarker Research group) has been developed as a positron emitting radiopharmaceutical for *in vivo* imaging of tau protein aggregates (Xia et al., 2013). Autoradiography results using tissue sections from human brains showed a strong signal in the grey matter of cortical slices from tau positive brains but weak or no binding in tau negative, Aβ positive, or tau and Aβ negative tissue. Scatchard analysis based on this heterogeneous autoradiography assay yielded an estimated K_d of 15nM. A saturation binding experiment using purified Paired Helical Fragment Tau isolated brains of AD patients yielded a K_d value of 0.54 nM.

An updated summary of preclinical and clinical experience pertaining to the safety of flortaucipir (^{18}F) can be found in the investigator's Brochure. Briefly, preclinical toxicity studies of 19F-AV-1451 (non-radioactive flortaucipir (^{18}F), "AV-1451") showed a good safety profile with no observable effects at high multiples of the intended maximum

human dose. AV-1451 was positive in the in vitro hERG assay. However, the cardiovascular assessments performed during the dog toxicology studies showed no evidence that AV-1451 prolongs the QT interval at high multiples of relevant clinical doses, and therefore the risk of QT prolongation is not included in the risk profile.

Human dosimetry results for flortaucipir (^{18}F) showed both hepatobiliary and renal excretion, and total effective dose similar to other approved F-18 radiopharmaceuticals. The organs of the gastrointestinal tract (upper large intestine, small intestine, and liver) received the greatest exposure. The whole body effective dose for a 10 mCi (370 MBq) dose of flortaucipir (^{18}F) was calculated to be 8.70 mSv. In human clinical studies so far, flortaucipir (^{18}F) is generally well-tolerated with a low incidence of mild and transient adverse events.

Image assessment showed tracer deposition on brain PET scans to be consistent with that expected for a tracer of aggregated tau protein. Flortaucipir (^{18}F) initially entered the brain and was subsequently eliminated from the brain in clinically normal and amyloid negative cognitively impaired subjects, yielding only a diffuse pattern of background activity, whereas a regionally distinct gray matter distribution of increased tracer retention was observed in amyloid positive cognitively impaired subjects (Pontecorvo et al., 2017). Preliminary analyses of our Phase II longitudinal study (A05, exploratory cohort) also indicate a relationship between the level and pattern of flortaucipir uptake at baseline, and the rate of decline on cognitive tests over an 18 month period (Mintun, AAIC 2017). These results suggest that it may be possible to use flortaucipir PET scans to enrich clinical studies for subjects with a desired level of AD pathology and a more homogeneous rate of cognitive decline, thus increasing power to detect a treatment effect. Specifically, Lilly and Avid desire to conduct treatment trials at the earliest stage of AD neuropathology to maximize potential patient benefit.

Proposed Lilly AD therapeutic trials intend to target patients with a certain distribution and density of tau neurofibrillary tangles that are hypothesized to be appropriate for certain trials. It is thought that patients with no tau will progress so slowly that a clinical treatment effect could not be discerned, and those with a large tau burden may not be responsive to anti-amyloid or anti-tau therapies as their cognitive impairment is driven primarily by tau pathology. The overarching goal of this protocol is to test this hypothesis by pre-screening patients with flortaucipir F 18 who have been diagnosed with suspected Alzheimer's disease and have indicated their interest to consider participation in Lilly therapeutic clinical trials.

2. STUDY OBJECTIVES

The primary objective is to pre-screen patients via a flortaucipir F 18 scan, who have objectively verified cognitive impairment and etiology diagnosed or suspected to be Alzheimer's disease, and have indicated their interest in participating in Lilly sponsored trials that require tau imaging for inclusion.

The secondary objective of the study is to expand the flortaucipir F 18 safety database.

3. SPONSOR, INVESTIGATOR(S) AND OTHER PARTICIPANTS

The study is sponsored by:

Avid Radiopharmaceuticals, Inc.

[redacted]

The medical contact is:

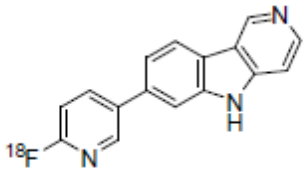
[redacted]

Approximately 10 centers in North America will participate.

4. TEST DRUG AND CONTROL AGENTS

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

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



MW = 262.27 amu

4.2. Radioactive Labeling

The 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.

4.3. Decay Characteristics

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

Min.	Fraction Remaining
0	1.000
30	0.827
60	0.685
90	0.567
120	0.469
150	0.388
180	0.321
210	0.266
240	0.220

Physical decay chart for Fluorine [^{18}F]. Half-life = 109.77 min.

4.4. Packaging flortaucipir F 18 Injection

Each package of flortaucipir F 18 Injection includes a sterile apyrogenic sealed glass vial or sterile apyrogenic syringe containing flortaucipir F 18 Injection, a surrounding protective lead shield canister, and an outside delivery case.

4.5. Storage and Handling flortaucipir F 18 Injection

Flortaucipir F 18 Injection is stored at room temperature. Flortaucipir F 18 Injection should be stored within the original container or equivalent radiation shielding.

5. INVESTIGATIONAL PLAN

5.1. Overall Design and Plan of the Study

Study ^{18}F-AV-1451-A24 is a multicenter screening study in patients with early symptomatic AD (defined as prodromal AD and mild dementia due to AD).

All patients will provide informed consent before starting any study procedures. This pre-screening study targets patients who are interested in participating in AD therapeutic clinical trials and have expressed a preliminary interest in a trial like the LMDC trial, and who are not known to meet any of the exclusion criteria for trials like LMDC based on medical history and clinical examination. However, consent for this protocol does not constitute consent for the LMDC trial or any other trials, and subjects who qualify for this protocol may still fail to qualify for trials like LMDC or other trials based on the results of this protocol or based on additional testing performed in those subsequent trials.

Screening assessments will include demographic information, cognitive testing, disease history, concomitant medications, vital signs, ECG and medical history. Patients who are deemed eligible to continue will complete a flortaucipir F 18 PET scan.

Patients who meet eligibility criteria will participate in this protocol until they have completed their flortaucipir F 18 PET scan, or they discontinue, withdraw consent, or if the sponsor decides to end this protocol early.

5.2. Planned Dosage and Duration of Treatment

5.2.1. Flortaucipir F 18 Dosage and Administration

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

5.2.2. Rationale for Dosages

Flortaucipir F 18 will be administered IV in a radioactive dose of 370 MBq (10mCi) 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 8.70 mSv for an anticipated 370 MBq (10 mCi) injection and is comparable to the effective dose of approved 18F-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

5.3.1 Inclusion Criteria

Patients must meet the following criteria to enroll in this study:

1. Men or women, at least 60 to 85 years of age at the time of consent;
2. Patients with gradual and progressive change in memory function reported by the patient or informant for ≥6 months;
3. Patients who have a MMSE score between 20-28 inclusive; performed using Serial-7's.
4. Patients who are willing to undergo a PET scan using flortaucipir F 18;
5. Patients who give informed consent or have a legally authorized representative (LAR) available to consent at the time of enrollment; and
6. A study partner who must be available if the patient enters the treatment trial.

5.3.2 Exclusion Criteria

Patients who meet any of the following criteria are not eligible to enroll:

Medical Conditions

1. 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 β-HCG at screening and negative urine β-HCG prior to flortaucipir F 18 injection) or breastfeeding at screening. Females should agree to avoid becoming pregnant by refraining from sexual activity or using reliable contraceptive methods for 24 hours following administration of flortaucipir F 18 injection;
2. Patients who lack, in the investigator's opinion, adequate premorbid literacy, adequate vision, or adequate hearing to complete the required psychometric testing;
3. Have significant neurological disease affecting the CNS, other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson's disease, multiple concussions, or epilepsy or recurrent seizures (except febrile childhood seizures);
4. Patients with any current primary psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the patient's ability to complete the study [Patients with history of schizophrenia or other chronic psychosis are excluded.];
5. Have a current serious or unstable illness including, cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with the analyses in this study; or has a life expectancy of <24 months;
6. Has a history of cancer within the last 5 years, with the exception of non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, non-progressive prostate cancer, or other cancers with low risk of recurrence or spread;

7. Have a past history (suspected or confirmed) of Hepatitis B or Hepatitis C;
8. Are clinically judged by the investigator to be at serious risk for suicide as assessed by medical history, examination, or the C-SSRS.
9. Have a history of alcohol or drug disorder (except tobacco use disorder) within 2 years before the screening visit;
10. Have a history of clinically significant multiple or severe drug allergies or severe post treatment hypersensitivity reactions (including but not limited to erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and/or exfoliative dermatitis)
11. Have known positive serologic findings for human immunodeficiency virus (HIV) antibodies. Local laws and regulations may apply to whether testing is required.

Magnetic Resonance Imaging, Vital Signs, Electrocardiograms, Laboratory Tests, and Physical Examination

12. Has previous MRI evidence of significant abnormality that would suggest another potential etiology for progressive dementia or a clinically significant finding that may impact the patient's ability to safely participate in the study;
13. Have any contraindications for MRI, including claustrophobia or the presence of contraindicated metal (ferromagnetic) implants/cardiac pacemaker;
14. Have any clinically important abnormality at screening, as determined by investigator, in physical or neurological examination, vital signs, ECG, or clinical laboratory test results that could be detrimental to the patient, could compromise the study, or show evidence of other etiologies for dementia.

Procedural

15. Has hypersensitivity to flortaucipir F 18 or any of its excipients;
16. Intend to use drugs known to significantly prolong the QT interval within 14 days or 5 half-lives, whichever is longer, of a scheduled screening/baseline flortaucipir F 18 PET scan, or have medical history of risk factors for torsades de pointes.
17. Have an ECG corrected QT (QTcF) interval measurement >450 msec (men) or >470 msec (women) at screening (as determined at the investigational site).
18. Have poor venous access;
19. Contraindication to PET;
20. Present or planned exposure to ionizing radiation that, in combination with the planned administration of study PET ligands, would result in a cumulative exposure that exceeds local recommended exposure limits.

Prior/Concurrent Clinical Trial Experience/ Other Exclusion

21. Patients that are currently enrolled in any other interventional clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
22. Have participated, within the last 30 days in a clinical trial involving an investigational product. If the previous investigational product is scientifically or medically incompatible with this study and has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to screening (Participation in observational studies may be permitted upon review of the observational study protocol and approval by the sponsor).
23. Are investigator site personnel directly affiliated with this study and/or their immediate families; immediate family is defined as spouse, parent, child, or sibling whether biological or legally adopted;
24. Are Lilly employees or are employees of third-party organizations (TPOs) involved in a study that requires exclusion of their employees;
25. In the opinion of the investigator, are otherwise unsuitable for a study of this type.

Prior/Concomitant Therapy

26. Have received treatment with a stable dose of an acetylcholinesterase inhibitor (AChEI) and/or memantine for less than 1 months [If a patient has recently stopped an AChEI and/or memantine, he or she must have discontinued treatment at least 1 months prior].
27. Have changes in concomitant medications that could potentially affect cognition and their dosing should be stable for at least 1 month before screening, (does not apply to medications with limited duration of use, such as antibiotics).
28. Have received active immunization agents for the treatment of Alzheimer's Disease
29. Have known allergies to LY3303560, related compounds, or any components of the formulation; or history of significant atopy
30. Have allergies to either monoclonal antibodies, diphenhydramine, epinephrine, or methylprednisolone;
31. Are receiving IgG therapy (also known as gamma globulin or intravenous immunoglobulin [IVIG])

5.3.3. Prior and Concomitant Therapy

All medications that are continued from the start of the study or that are started during the study (other than the study medication) must be documented in the case record form on the Concomitant Medication Page of the Case Record Form (CRF).

5.4 Removal of Subjects from Study

Subjects must be removed from the study 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 study.

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

5.5 Premature Termination of Study/Closure of Center

The sponsor may discontinue the pre-screener at any time. Reasons for discontinuation may include, but are not limited to requests from regulatory authorities, safety or changes in business priorities. Reasons for center closure may include, but are not limited to, excessive protocol violations, inadequate regard for patient safety, failure to follow recommended procedures (e.g., documentation), failure or inability to accommodate Avid/Contract Research Organization (CRO) or to provide required access to data and source documents, staff turnover, inadequate staffing, and inadequate enrollment.

6. WARNINGS/PRECAUTIONS

The most up-to-date and complete information regarding the use of flortaucipir F 18 injection can be found in the investigator's brochure.

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

7. PROCEDURES AND METHODS

7.1. Assessment Periods

See Section 11.2, Study Flow Charts.

7.1.1. Screening Visit:

Screening may take place over several days. All screening assessments will be performed within approximately 30 days prior to flortaucipir F 18 injection.

Screening assessments will include:

- Informed consent for patient;
- Demographics (age, gender, years of education, race, ethnicity); weight/height; Weight will be collected during the imaging visit.
- Medical history, concomitant medications;
- Vital Signs (pulse, respiration rate, supine blood pressure)
- An ECG will be performed to assess the participant's cardiac status. If an ECG was performed within the last 12 months of the flortaucipir (^{18}F) PET Imaging Visit and is available for review, the ECG does not need to be repeated.
- ApoE status, if available;
- Disease history (date/months since symptom onset, date/months since diagnosis, family history of relevant neurologic disease);
- Cognitive status interview, including MMSE, performed using Serial-7's and CBB;
- A physician will see the patient during the screening visit.
    - Note: A physician will see the patient during the screening visit. However individual screening assessments may be delegated to a designee by the PI.
- For women of childbearing potential, a negative serum pregnancy test must be obtained at the screening visit.

7.1.2. Imaging Visit

Flortaucipir F 18 PET Imaging 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 and/or evaluate the subject prior to administration of flortaucipir F 18 to determine if they are still suitable to undergo the scan. If a designee performs this activity, a physician must be available to provide medical consultation;

- For women of childbearing potential, a negative urine pregnancy test (HCG) must be obtained within 24 hours prior to flortaucipir F 18 dose administration;
- Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of flortaucipir F 18 injection followed by a saline flush. The volume of flortaucipir F 18 dose should not be adjusted by adding normal saline to the syringe per the Investigator's Brochure.
- 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 at the injection site;
- Adverse events will be continuously monitored during the flortaucipir 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 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 and/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/study partner 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 patients and their LAR, if applicable, will be allowed to read a written informed consent form. The principal investigator, or designee, will explain all procedures, risks, and alternatives to the patient and LAR, if applicable. The patient and LAR, if applicable, 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 pre-screener (*see* Section 7.5). A copy of the signed informed consent will be given to the patient and study partners.

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 physician or PI designee will obtain an updated history at the screening visit.

- Relevant demographic information
- Diagnosis
- Review of body systems
- Social history
- Medical and surgical history
- History/results of genetic testing relevant to AD
- Concurrent medications

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

Physician Visit

A physician will 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 and/or evaluate the subject prior to administration of flortaucipir F 18 injection and prior to discharge from the imaging center. If a designee performs this activity, a physician must be available to provide medical consultation. At discharge, the physician or licensed/credentialed medical professional should review all safety data and briefly examine/query the subject regarding potential adverse events or other treatment issues.

Pregnancy Testing

Serum beta hCG, qualitative: performed at screening for females of childbearing potential only.

Women who are not of childbearing potential are defined as those who are:

a. Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation),
b. Post-menopausal – defined as either
    i. A woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
    ii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Urine beta hCG: performed within 24 hours prior to injection at the flortaucipir F 18 imaging visit for females of childbearing potential (defined as pre-menopausal, less than 2 years post-menopausal or not surgically sterile).

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. For this study, all patients will complete a MMSE, performed using Serial-7's. Patients need to score between 20-28 inclusive, to be eligible for the study.

CogState Brief Battery (CBB)

The CBB will be administered to patients at screening in addition to the MMSE. The CBB is a brief (15-18 minute), computer-based cognitive test battery designed to measure psychomotor function, attention, working memory and memory (Maruff et al. 2009, 2013; Fredrickson et al. 2010;Darby et al. 2012). The CBB has been shown to be sensitive to AD-related cognitive decline in healthy older adults and in adults with amnestic MCI (Darby et al. 2002, 2012; Lim et al. 2013a, b) as well as to improvement in cognition arising from treatment with cognitive enhancing drugs (Davison et al. 2011; Jaeger et al. 2011; Nathan et al. 2013). The CBB will be administered at screening in an effort to further characterize patients enrolled in the study.

Electrocardiogram (ECG)

A resting 12-lead electrocardiogram will be recorded as part of the screening visit, unless an ECG was performed within twelve months of the anticipated flortaucipir (^{18}F) PET Imaging Visit and is available for review.

Vital Signs

Vital signs (pulse rate, respiratory rate, and supine blood pressure) will be taken at the Screening Visit. Weight will be measured, lightly clothed during the imaging visit. Height will be obtained during the screening visit.

7.3. Protocol for Image Collection

An imaging manual will be created for the flortaucipir F 18 PET scan procedures and distributed to participating imaging centers prior to site initiation.

Required scan data sets and transmission instructions will be provided to the PET centers for all scans acquired under this protocol.

PET scan images must be de-identified and assigned a unique patient number prior to submission to Avid.

Feedback regarding the flortaucipir F 18 scan will be provided to the investigator, inclusive of any incidental findings

7.4. Good Clinical Practice and Monitoring

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

This includes:

1. IRB/IEC approval: An investigation will be initiated at a study site only after the IRB/IEC for that study site has given their written approval of the protocol and informed consent;
2. Informed Consent: Study procedures will not be initiated until the subject and/or their legally authorized representative (as appropriate) signs the informed consent form;
3. Recording and monitoring of adverse events as outlined in Section 7.7.3 including the notification of study site clinical investigators, local IRBs and the FDA regarding serious adverse event;
4. Avid RP's obligation to monitor the participating center on a regular basis;
5. Avid RP's obligation to audit the participating center, as needed; and
6. The termination of a center or the study if conditions apply, as outlined in Section 5.5.

7.5. Informed Consent and Subject Information

Potential subjects, or their legally authorized representative (as appropriate), will be allowed to read a written informed consent form. The principal investigator or designee will explain all study procedures, risks, and alternative therapies. The subject and legally authorized representative will have an opportunity to have all questions answered by a physician. The subject will then sign and date the informed consent form, indicating willingness to participate in the study.

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

If the subject is not capable of giving consent, consent may be given by a legally authorized representative. However, it is expected that all subjects entering this study should at least have the capacity to understand that they are engaging in a research study and should affirm that they do not object to participating, by signing on the Subject Assent line of the consent form.

All informed consent forms must be approved by Avid or designee, and by the appropriate Institutional Review Board (IRB). No study related procedures shall be

performed prior to completion of the informed consent process, and signing of the consent form. A copy of the signed informed consent should be given to the patient and/or their legally authorized representative for their records.

7.6. Documentation

Flortaucipir F 18 PET scans will be saved in an appropriate electronic format as specified in the imaging manuals. A copy of all scans will be saved at the site/imaging center and a copy of each will be forwarded to Avid 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 patient's medical files, 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").

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 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/or 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.

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 flortaucipir F 18, and thus be reported as treatment-emergent adverse events, if they occur within 48 hours after flortaucipir F 18 administration.

The end of study, for the purpose of adverse event reporting, is defined as 48 hours after the last administration of flortaucipir F 18.

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

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

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

investigator feels the events were related to either investigational product or a protocol procedure.

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

8. STATISTICAL ANALYSIS

8.1. General Statistical Considerations

Patients' demographic and baseline characteristics data will be summarized using descriptive statistics (number of patients [N], mean, standard deviation [SD], median, quartiles, minimum, and maximum) for continuous variables and using frequency count and percentage for discrete variables.

Patient listings of all data from the eCRFs as well as any derived variables will be presented.

8.1.1. Population for Analysis

The safety analysis population will include all eligible patients who enroll in ^{18}F-AV-1451-A24 (A24) and have received at least one dose of flortaucipir F 18 injection. Efficacy analysis population will include all subjects in safety population, and with a valid flortaucipir F 18 scan assessment (quantitative and/or qualitative).

8.2. Analysis

Descriptive analyses will be applied to summarize patients' demographic and baseline characteristics, and qualitative and quantitative assessments of the flortaucipir F 18 PET image.

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.

9. USE OF DATA AND PUBLICATION

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

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

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

10. INVESTIGATOR'S REGULATORY OBLIGATIONS

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

10.1. Institutional Review Board (IRB)

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

10.2. Informed Consent

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

10.3. Protocol Adherence

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

10.4. Documents Necessary for Initiation of the Study

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

- Original signed and dated Statement of Agreement page;
- Copy of the IRB/IEC and radiation safety committee approval (if applicable);
- Copy of the IRB/IEC stamped approved consent form;
- Name and location of the laboratory utilized for laboratory assays, and other facilities conducting tests, including laboratory certification number and date of certification if available. Avid may be responsible for supplying these to the investigator if a central laboratory is used;
- List of reference range laboratory values. Avid may be responsible for this if a central laboratory is used; and
- Any additional licenses required in order to order flortaucipir F 18.

10.5. Investigational Product Control

The receipt of clinical supplies (i.e. starting material for flortaucipir F 18) 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. Flortaucipir F 18Injection should be prepared by a qualified PET manufacturing site and administered by a qualified individual under the investigator's supervision. An up-to-date drug inventory/dispensing record must be maintained. All drug supplies must be accounted for. After completion of the trial, all remaining clinical supplies must be returned to the sponsor or their representative.

10.6. Data Collection

Electronic case report forms (eCRFs) will be used for this study. 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 study is completed, the informed consent form should be kept on file with other study 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 study. The eCRFs must be completed for each patient enrolled in the study and signed by the investigator. This should be done as soon as possible after completion of the patient's participation in the study. 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.

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

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

10.8. Records Retention

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

Alaka K, Campbell G, Fleisher A, Hake A, Irizarry M, Miller B, Pontecorvo M, Siemers E, Sims J, Yaari R. The nosology of Alzheimer's disease and application of concepts to amyloid-targeting treatments: an internal summary of Lilly thinking. White Paper. 2015.

Albert, M. S., DeKosky, S. T., Dickson, D., et al. "The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup." The Alzheimer's Association. Alzheimer's and Dementia, 1-10, 2011.

Burack, M.A., Hartlein, J., Flores, H.P., Taylor-Reinwald, L., Perlmutter, J.S., Cairns, N.J. "In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia". Neurology. 2010;74(1):77-84.

Chien, D.T., Bahri, S., Szardenings, A.K., Walsh, J.C., Mu, F., Su, M.Y., Shankle, W.R., Elizarov, A., Kolb, H.C., "Early clinical PET imaging results with the novel PHF-tau radioligand [18F]-T807." J Alzheimers Dis, 2013 Jan 1l34(2):467-68

Clark, C.M., Pontecorvo, M.J., Beach, T.G., Bedell, B.J., Coleman, R.E., Doraiswamy, P.M., Fleisher, A.S., Reiman, P.E.M., Sabbagh, M.N., Sadowsky, C.H., Schneider, J.A., Arora, A., Carpenter, A.P., Flitter. M.L., Joshi, A.D., Krautkramer, M.J., Lu, M., Mintun, M.A., Skovronsky, D.M. "Florbetapir PET for Detection of Amyloid Neuritic Plaques, Comparison to Neuropathology at Autopsy: A Prospective Cohort Study." The Lancet Neurology, 2012; 11: 669–78.

Clark, C.M., Schneider, J.A., Bedell, B.J., et al. "Use of florbetapir-PET for imaging beta-amyloid pathology". JAMA. 2011;305(3):275-283.

Darby, D, Maruff, P, Collie, A, McStephen, M. Mild cognitive impairment can be detected by multiple assessments in a single day. *Neurology*. 2002;59(7):1042-1046.

Darby DG, Pietrzak RH, Fredrickson J, Woodward M, Moore L, Fredrickson A, Sach J, Maruff P. Intraindividual cognitive decline using a brief computerized cognitive screening test. *Alzheimers Dement*. 2012;8(2):95-104.

Davison SL, Bell RJ, Gavrilescu M, Searle K, Maruff P, Gogos A, Rossell SL, Adams J, Egan GF, Davis, SR. Testosterone improves verbal learning and memory in postmenopausal women: results from a pilot study. *Maturitas*. 2011;70(3):307-311.

Dickson, T.C., Saunder, H.L., Vickers, J.C. "Relationship between apolipoprotein E and the amyloid deposits and dystrophic neuritis of Alzheimer's disease." Neuropathol Appl Neurobiol. 1997; (23):483-491.

Dubois B., Feldman H.H., Jacova C., et al. "Revising the definition of Alzheimer's disease: a new lexicon". Lancet Neurol. 2010;9(11):1118-1127.

Duyckaerts, C., Brion, J.P., Hauw, J.J., Flament-Durand, J. "Quantitative assessment of the density of neurofibrillary tangles and senile plaques in senile dementia of the

Alzheimer type. Comparison of immunocytochemistry with a specific antibody and Bodian's protargol method." Acta Neuropathol. 1987;(7):129-135.

Folstein, M.R., Folstein, S.E., and McHugh, P.R. "Mini Mental State: A practical method for grading the cognitive status of patients for the clinician." Journal of Psychiatric Research, 12: 189-198, 1975.

Fredrickson J, Maruff P, Woodward M, Moore L, Fredrickson A, Sach J, Darby D. Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. *Neuroepidemiology*. 2010;34(2):65-75.

Hyman, B.T., Phelps, C.H., Beach, T.G., et al. "National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease". Alzheimers Dement. 2012;8(1):1-13.

Jack, C.R., Knopman, D.S., Jagust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., Petersen, R.C., Trojanowski, J.Q. "Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade." Lancet Neurol 9:119-128, 2010.

Jaeger, J, Hårdemark, H-G, Zettergren, A, Sjögren, N, Hannesdottir, K. Does repeated daily testing improve measurement sensitivity to the cognitive effects of donepezil in mild-to-moderate Alzheimer's Disease? *Alzheimer's & Dementia*. 2011:7(4):e59. (Paper presented at the Alzheimer's Association International Conference, Paris, France).

Kantarci, K., Lowe, V.J., Boeve, B.F., Weigand, S.D., Senjem, M.L., Przybelski, S.A., et al. "Multimodality imaging characteristics of dementia with Lewy bodies". Neurobiol Aging 2011: Oct 20. [Epub ahead of print].

Leinonen, V., Alafuzoff, I., Aalto S., Suotunen, T., Savolainen, S., Nagren, K., et al. "Assessment of beta-amyloid in a frontal cortical brain biopsy specimen and by positron emission tomography with carbon 11-labeled Pittsburgh Compound B". Arch Neurol 2008; 65(10):1304–1309.

Lim YY, Ellis KA, Ames D, Darby D, Harrington K, Martins RN, Masters CL, Rowe C, Savage G, Szoeke C, Villemagne VL, Maruff P; AIBL Research Group. Aβ amyloid, cognition, and APOE genotype in healthy older adults. *Alzheimers Dement.* 2013a;9(5):538-545.

Lim YY, Ellis KA, Harrington K, Pietrzak RH, Gale J, Ames D, Bush AI, Darby D, Martins RN, Masters CL, Rowe CC, Savage G, Szoeke C, Villemagne VL, Maruff P, for the AIBL Research Group. Cognitive decline in adults with amnestic mild cognitive impairment and high amyloid β amyloid: prodromal Alzheimer's disease? *J Alzheimers Dis.* 2013b;33(4):1167-1176.

Maruff P, Thomas E, Cysique L, Brew B, Collie A, Snyder P, Pietrzak RH. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. *Arch Clin Neuropsychol.* 2009;24(2):165-178.

Maruff P, Lim YY, Darby D, Ellis KA, Pietrzak RH, Snyder PJ, Bush AI, Szoeke C, Schembri A, Ames D, Masters CL, AIBL Research Group. Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. *BMC Psychol.* 2013;1(1):30.

McKhann, G.M., Knopman, D.S., Chertkow, H., et al. "The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease". Alzheimers Dement. May 2011;7(3):263-269.

Mintun MA, Devous MD, Lu M, Pontecorvo MJ, Joshi AD, Southekal S, Siderowf A, Lowrey MJ, Devine M, Benedum TE, Pearson C, Lim NC, Case MG, L Sundell K, Siemers E. PET biomarkers in the EXPEDITION 3 trial of patients with Mild AD. Alzheimer's Association International Congress, July 2017, London UK

Nathan, PJ, Boardley, R, Scott, N, Berges, A, Maruff, P, Sivananthan, T, Upton N, Lowy MT, Nestor PJ, Lai, R. The safety, tolerability, pharmacokinetics and cognitive effects of GSK239512, a selective histamine H3 receptor antagonist in patients with mild to moderate Alzheimer's disease: a preliminary investigation. *Curr Alzheimer Res*. 2013;10(3):240-251.

Pontecorvo MJ, Devous MD Sr, Navitsky M, Lu M, Salloway S, Schaerf FW, Jennings D, Arora AK, McGeehan A, Lim N, Xiong H, Joshi AD, Siderowf A, Mintun MA for the ^{18}F-AV-1451-A05 Investigators. Relationships between Flortaucipir (^{18}F-AV-1451) Positron Emission Tomography Tau Binding and Amyloid Burden Clinical Diagnosis, Age and Cognition. Brain. 2017; 140:748-763.

Price, J.L., Morris, J.C. "Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease." Ann Neurol 45:358–368, 1999.

Sojkova J., Driscoll I., Iacono D., Zhou Y., Codispoti K., Kraut M., et al. "In vivo fibrillar beta-amyloid detected using [11C] PiB positron emission tomography and neuropathologic assessment in older adults". Arch Neurol 2011;68(2):232–240.

Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack, C.R., Jr., Kaye, J., Montine, T.J., Park, D.C., Reiman, E.M., Rowe, C.C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M.C., Thies, B., Morrison-Bogorad, M., Wagster, M.V., Phelps, C.H. 2011. "Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease". Alzheimer's Dement 7(3), 280-92.

Wong, D.F., Rosenberg, P.B., Zhou, Y., et al. "In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir [corrected] F 18)". J Nucl Med. 2010;51(6):913-920.

Xia, C.F., et al. "[18F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease," Alzheimer's Dement. 2013, 1-11

11.2. Study Flow Chart

Evaluations/Procedures	Screening Visit [a]	Flortaucipir F 18 Imaging Visit	End of Flortaucipir F 18 Imaging (prior to discharge)	Follow-up Phone Call
Signed Consent	X			
Demographics	X			
Medical History/Neurologic Disease History	X			
Concomitant Meds	X	X		
Vital Signs [b]	X			
ECG	X			
MMSE and CBB [c]	X			
Serum beta-hCG [d]	X			
Urine Pregnancy Test[e]		X		
flortaucipir F 18 scan		X		
Evaluation by a physician [f]	X	X	X	
Adverse Events	X	X	X	X
Serious Adverse Events	X	X	X	X

a. Screening may take place over several days. All assessments must be performed within approximately 30 days of the ^{18}F-AV-1451 imaging session.
b. Vital signs (pulse, respiratory rate, supine blood pressure). Weight will be taken at the imaging visit.
c. All patients will complete the MMSE, performed using Serial-7's, followed by the CBB.
d. Serum beta-hCG pregnancy test at screening for females of childbearing potential.
e. For women of childbearing potential, a negative urine pregnancy test must be obtained within 24 hours prior to the flortaucipir F 18 injection.
f. A physician must see the patient during screening. For the imaging visit, a physician or PI designee may evaluate the patient.

12. INVESTIGATOR'S AGREEMENT TO PROTOCOL

Protocol: ^{18}F-AV-1451-A24
A multicenter screening study with flortaucipir F 18 in patients with early symptomatic AD; #2

Date and Version: Amendment #1; 17APR18

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