Protocol Number:
^{18}F-AV-1451-A20

Date and Version:
20 January 2017
Amendment 1

Name of Compound:
flortaucipir (^{18}F) Injection

Sponsor:
Avid Radiopharmaceuticals
Philadelphia, Pennsylvania USA

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

Title of Study: "Flortaucipir (^{18}F) PET Imaging in the BIOCARD Study"

Planned number of subjects (Enrolled): Approximately 100

Subjects will be recruited from the pool of participants in the Biomarkers of Cognitive Decline Among Normal Individuals study (BIOCARD) being conducted at Johns Hopkins University. The overall recruitment goal is that 80 percent of subjects are amyloid positive, and 20 percent are amyloid negative.

Name of compound: flortaucipir (^{18}F) Injection (also known as ^{18}F-AV-1451)
Dose*:* 370 MBq (10 mCi)
Route of Administration: Intravenous (IV) bolus

Study Phase: I

Study Centers: 1 center in the United States

Trial Objectives:

The primary objectives of this study are:

- To evaluate imaging characteristics of flortaucipir (^{18}F) in respect to brain amyloid status in subjects who are enrolled in the BIOCARD study
- To examine the relationship between cognitive and functional performance, other biomarker data, and tau deposition as measured by flortaucipir (^{18}F) uptake in clinically normal subjects

A secondary objective of this study is:

- To expand the flortaucipir (^{18}F) safety database.

Eligibility:

Only subjects duly consented and enrolled in the BIOCARD protocol (conducted by Johns Hopkins University with Dr. Marilyn Albert as Principal Investigator) will be considered for participation in this study (see Section 5.3, Selection of Subjects).

Study Design:

This is a phase I study that will evaluate imaging characteristics of flortaucipir (^{18}F) in subjects enrolled in the BIOCARD study.

Subjects enrolled in the BIOCARD study will be contacted to participate and must provide informed consent before starting any AV-1451-A20 study procedures. In addition to consenting to study procedures, participants will consent to have Magnetic Resonance Imaging (MRI) images/data, laboratory data, medical and neuropsychological assessments, as well as amyloid

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

status, and lumbar puncture results made available to this study to allow for analysis and comparison. This study hopes to recruit roughly 80 percent amyloid positive subjects, and 20 percent amyloid negative subjects from the BIOCARD study. Amyloid positivity will be determined by quantification of the BIOCARD PiB scan, and a list of patients for recruitment blinded to amyloid status will be provided to the site. Subjects' amyloid status will not be revealed as a part of recruitment or inclusion for this study.

Screening assessments may take place over several days, within 90 days of the flortaucipir (^{18}F) Positron Emission Tomography (PET) scan, and will include demographics, medical history and concomitant medications, a physical exam, and a safety evaluation. Additionally, participants will have an ECG with results reviewed prior to the initial flortaucipir (^{18}F) imaging visit. If the ECG was performed within the last six to twelve months of the ^{18}F -AV-1451 PET Imaging Visit and is available for review, the ECG does not need to be repeated. Subjects may be permitted to return for the flortaucipir (^{18}F) PET scan after the 90 day window with sponsor approval if the investigator does not recognize any significant medical changes.

Subjects who qualify for the study will return to the clinic at a later date for the flortaucipir (^{18}F) PET imaging visit. For the flortaucipir (^{18}F) PET imaging visit, an intravenous catheter will be placed for IV administration of flortaucipir (^{18}F) injection. Subjects will receive a single IV bolus injection with a target dose of 370 MBq (10 mCi) of flortaucipir (^{18}F) 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.

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.

Assessments and Endpoints:

All subjects will have a screening visit, a flortaucipir (^{18}F) 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:

Exploratory analyses will examine the relationship among flortaucipir (^{18}F) SUVr measurements, cognitive and neuropsychiatric measurements, and other collected biomarkers in subjects.

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Additional retrospective analyses will be conducted to explore the possible risk factors of tau deposition.		

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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.
CRO	Contract Research Organization: A person or organization (commercial, academic, or other) contracted by the sponsor to perform one or more of the sponsor's trial-related duties and functions.
ECG	Electrocardiogram
Efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result.
EOS	End of Synthesis
FDA	US Food and Drug Administration

FDG	18F - 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
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
NOAEL	No Observable Adverse Effect Level

PET	Positron Emission Tomography
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
QTcB	Bazett's 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
SOC	System Organ Class
SUVr	Standard Uptake Value Ratio
TdP	Torsades de Pointes

1. INTRODUCTION

Of the 2 pathological protein deposits that are the hallmark of Alzheimer's disease (AD), beta- amyloid (Aβ) is thought to accumulate very early in the disease process and is frequently observed in elderly subjects with no clinical symptoms, a condition that may represent a preclinical phase of the disease. Furthermore, as a biomarker, Aβ plaques as seen on PET amyloid imaging appear to plateau in intensity early in the symptomatic phase of the disease.

In contrast to Aβ deposits, the density and distribution in the brain of phosphorylated tau, in the form of neocortical tangle pathology, has been shown in autopsy studies to be increased with AD-related cognitive impairment and appears to correlate with overall evidence of neurodegeneration across the entire spectrum of the illness (Duyckaerts et al. 1987; Nelson et al. 2012). Thus, an understanding of the onset and progression of tau pathology in relation to amyloid pathology and cognitive change may be critical to understanding the course of the disease.

Flortaucipir (^{18}F) (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 Kd 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 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 risk of QT prolongation is not included in the risk profile. Nonetheless, until sufficient human cardiovascular safety data are available, 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.

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.

Preliminary 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 normal subjects yielding only a diffuse pattern of background activity, whereas a regionally distinct gray matter distribution of increased tracer retention was observed in subjects with high probability AD. Interim cross-sectional efficacy results (study flortaucipir (^{18}F) -A05) show a distribution pattern of aggregated tau across diagnostic groups paralleling that hypothesized on the basis of postmortem evaluation (Braak et al., 2006).

A relatively small number of subjects in the ongoing A05 study presented cognitively as clinically normal with elevated brain amyloid. It is important to evaluate additional subjects of this type to obtain information regarding the presence/onset of tau pathology because clinically normal amyloid positive subjects have been hypothesized to represent the earliest preclinical stage of AD (Sperling et al., 2011). The present study will obtain flortaucipir (^{18}F) tau PET scans in 100 clinically normal subjects from the BIOCARD study that have been identified as having elevated brain amyloid by PET or CSF assays.

2. TRIAL OBJECTIVES

The primary objectives of this study are:

- To evaluate imaging characteristics of flortaucipir (^{18}F) in respect to brain amyloid status in subjects who are enrolled in the BIOCARD study
- To examine the relationship between cognitive and functional performance, other biomarker data, and tau deposition as measured by flortaucipir (^{18}F) uptake in clinically normal subjects

A secondary objective of this study is:

- To expand the flortaucipir (^{18}F) 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:

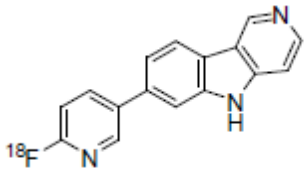
[redacted]

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

4. TEST DRUG AND CONTROL AGENTS

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

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



MW = 262.27 amu

4.2 Radioactive Labeling

The compound is labeled with [^{18}F] fluorine that decays by positron (β+) emission and has a half-life of 109.77 min. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron.

4.3 Decay Characteristics

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

Min.	Fraction Remaining
0	1.000
30	0.827
60	0.685
90	0.567
120	0.469
150	0.388
^{18}0	0.321
210	0.266
240	0.220

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

a. Formulation and Dose flortaucipir (^{18}F) Injection

Flortaucipir (^{18}F) injection is a sterile, apyrogenic clear solution for intravenous bolus administration. Flortaucipir (^{18}F) injection contains flortaucipir (^{18}F) (drug substance) formulated in 10% (v/v) ethanol, USP in 0.9% sodium chloride injection, USP.

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

b. Packaging flortaucipir (^{18}F) Injection

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

4.6 Storage and Handling flortaucipir (^{18}F) Injection

Flortaucipir (^{18}F) injection is stored at room temperature. Flortaucipir (^{18}F) injection should be stored within the original container or equivalent radiation shielding.

5. INVESTIGATIONAL PLAN

5.1 Overall Design and Plan of Trial

This is a phase I study that will evaluate imaging characteristics of flortaucipir (^{18}F) in subjects enrolled in the BIOCARD study.

Subjects enrolled in the BIOCARD study will be contacted to participate and must provide informed consent before starting any AV-1451-A20 study procedures. In addition to consenting to study procedures, participants will consent to have BIOCARD-related data, including Magnetic Resonance Imaging (MRI) images/data, laboratory data, medical and neuropsychological assessments, as well as amyloid status, and lumbar puncture results, made available to this study to allow for analysis and comparison. This study hopes to recruit roughly 80 percent amyloid positive subjects, and 20 percent amyloid negative subjects from the BIOCARD study. Amyloid positivity will be determined by quantification of the BIOCARD PiB scan, and a list of patients for recruitment blinded to amyloid status will be provided to the site. Subjects' amyloid status will not be revealed as a part of recruitment or inclusion for this study.

Screening assessments may take place over several days, within 90 days of the flortaucipir (^{18}F) Positron Emission Tomography (PET) scan, and will include demographics, medical history and concomitant medications, a physical exam, and a safety evaluation. Additionally, participants will have an ECG with results reviewed prior to the initial flortaucipir (^{18}F) imaging visit. If the ECG was

performed within the last six to twelve months of the ^{18}F -AV-1451 PET Imaging Visit and is available for review, the ECG does not need to be repeated. Subjects may be permitted to return for the flortaucipir (^{18}F) PET scan after the 90 day window with sponsor approval if the investigator does not recognize any significant medical changes.

Subjects who qualify for the study will return to the clinic at a later date for the flortaucipir (^{18}F) PET imaging visit. For the flortaucipir (^{18}F) PET imaging visit, an intravenous catheter will be placed for IV administration of flortaucipir (^{18}F) injection. Subjects will receive a single IV bolus injection with a target dose of 370 MBq (10 mCi) of flortaucipir (^{18}F) 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.

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.

5.2 Planned Dosage and Duration of Treatment

5.2.1 Dosage and Administration

All subjects will receive a single IV bolus administration of approximately 370 MBq (10 mCi) of flortaucipir (^{18}F) injection.

5.2.2 Rationale for Dosage

Flortaucipir (^{18}F) 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. Male or females that have consented and are currently enrolled in the BIOCARD protocol
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).

5.3.2 Exclusion Criteria

Subjects will be excluded from enrollment if they:
1. Has any condition by history or abnormal findings on physical examination or screening tests that, in the investigator's opinion, could increase risk to the participant, limit the participant's ability to tolerate the experimental procedures (e.g., chronic back pain which might limit the ability to lie still during the scanning procedures), or interfere with analysis of the data.
2. Has a history of risk factors for Torsades de Pointes or is taking medications known to prolong QT interval. A list of restricted medications will be provided.
3. Have ECG obtained prior to the initial flortaucipir (^{18}F) scan that in the opinion of the investigator is clinically significant with regard to the subject's participation in the study. Bazett's corrected QT (QTcB) interval must be evaluated and must not exceed 458 msec in males, or 474 msec in females.
4. Are females of childbearing potential who are not surgically sterile, not refraining from sexual activity or not using reliable methods of contraception. Females of childbearing potential must not be pregnant (negative serum β-hCG at the time of screening and negative urine β-hCG on imaging day) or breastfeeding at screening. Females must agree to avoid becoming pregnant, and refrain from sexual activity or to use reliable contraceptive methods for 24 hours following administration of flortaucipir (^{18}F).
5. Has hypersensitivity to flortaucipir (^{18}F) or any of its excipients.
6. 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;
7. Have had a non-study related radiopharmaceutical imaging or treatment procedure within 7 days prior to the flortaucipir (^{18}F) imaging session;
8. In the opinion of the investigator, are otherwise unsuitable for a study of this type.

a. 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 flortaucipir (^{18}F) injection can be found in the investigator's brochure.

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

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 BIOCARD study protocol will be contacted to participate. Screening assessments may take place over several days, within 90 days of the flortaucipir (^{18}F) PET scan, and will include:

- Informed Consent will take place before any AV-1451-A20 study procedures;
- Demographics (birth year, gender, race, ethnicity, education, alcohol, drug use and smoking);
- Medical history and concomitant medications;
- For women of childbearing potential, a negative serum pregnancy test must be obtained at the screening visit.
- A physician will see the subject during the screening assessments.
- 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.

7.1.2 Imaging Visit(s)

<u>Flortaucipir (^{18}F) 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 flortaucipir (^{18}F) injection to determine if they are still suitable to undergo the scan. If a designee performs this activity, a physician must be available to provide medical consultation;
- For women of childbearing potential, a negative urine pregnancy test must be obtained on the day of flortaucipir (^{18}F) dose administration;
- Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of flortaucipir (^{18}F) 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 flortaucipir (^{18}F) 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.

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.

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 flortaucipir (^{18}F) PET Imaging Visit and is available for review.

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 flortaucipir (^{18}F) 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 (defined as pre-menopausal, less than 2 years post-menopausal or not surgically sterile). A serum pregnancy test may also be obtained prior to injection at the imaging visit if required by the local site.
- Urine beta hCG: performed at the flortaucipir (^{18}F) imaging visit prior to injection for females of childbearing potential (defined as pre-menopausal, less than 2 years post-menopausal or not surgically sterile).

7.3 Protocol for Image Collection

The sponsor will prepare and distribute imaging manuals for flortaucipir (^{18}F) 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

Flortaucipir (^{18}F) 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 BIOCARD 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").

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 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 (^{18}F), and thus be reported as adverse events, if they occur within 48 hours after flortaucipir (^{18}F) administration.

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

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 the BIOCARD protocol, such as but not limited to subjects' demographic and baseline characteristics, medical history, neurological and behavioral evaluations, neuropsychological test results, MRI, and other biomarker studies will be transferred to Avid for analysis purposes.

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

8.2 Safety Analysis

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.

8.3 Image Analysis

All flortaucipir (^{18}F) 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.

8.4 Exploratory Analyses

Exploratory analyses will examine the relationship among flortaucipir (^{18}F) uptake measurements, cognitive and neuropsychiatric measurements, and other collected biomarkers in subjects, and will explore whether the flortaucipir (^{18}F) uptake measurements are correlated with other biomarkers, cognitive status, and clinical presentation. Additional retrospective analyses will be conducted to explore the possible risk factors of tau deposition.

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.

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 flortaucipir (^{18}F).

10.5 Study Drug Control

The receipt of clinical supplies (e.g. starting material for flortaucipir (^{18}F)) 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 (^{18}F) 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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Nelson, P.T., et al. ““Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature”. Journal of Neuropathology & Experimental Neurology. 2012, 362-381.

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Sperling, R.A., et al. “Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging and the Alzheimer’s Association workgroup”. Alzheimer’s & Dementia. 2011, 1-13.

Xia, C.F., et al. “[^{18}F]T807, a novel tau positron emission tomography imaging agent for Alzheimer’s disease”. Alzheimers Dement. 2013, 1-11.

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]
Signed Informed Consent	X			
Demographics	X			
Medical History	X			
Concomitant Medications	X			
ECG	X[c]			
PET Brain Scan		X [d, e]		
Evaluation by a physician	X	X[f]	X[g]	
Pregnancy Test	X[h]	X[i]		
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 90 days prior to the flortaucipir (^{18}F) imaging session. Subjects may be permitted to return for the flortaucipir (^{18}F) 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. ECG (with results reviewed prior to flortaucipir (^{18}F) administration).
d. Subjects will receive a single IV bolus injection target dose of 370 MBq (10 mCi) of flortaucipir (^{18}F) injection followed by a saline flush.
e. At approximately 75 minutes following flortaucipir (^{18}F) injection, a continuous 30-minute brain scan will begin.
f. 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.
g. Or physician designee.
h. Serum pregnancy test
i. Urine pregnancy test prior to flortaucipir (^{18}F) injection

INVESTIGATOR'S AGREEMENT TO PROTOCOL

Protocol ^{18}F-AV-1451-A20: "Flortaucipir (^{18}F) PET Imaging in the BIOCARD Study"

Date and Version: 20 JANUARY 2017
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