Protocol Title: **F 18 T807 tau PET imaging in familial amyotrophic lateral sclerosis (IND 123119, Protocol B)**

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Study Product: ^{18}F-AV-1451 (also known as [F-18]T807 or LY3191748)

Protocol: Protocol B

Version: 4

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IND Number: 123119

Revisions

Revision 3, 04/30/2018

1. Protocol version date and number were updated.
2. Additional study team list was deleted on page 6.
3. Research lab manager and Imaging Coordinator's information was deleted
4. The following was added to "Inclusion Criteria" #4: Females of childbearing potential without documented history of menopause or hysterectomy who do participate must not be pregnant or breastfeeding at screening (negative urine β-HCG within 24 hours prior to injection of radioactivity), and must agree to avoid becoming pregnant.
5. The following was added to "Exclusion Criteria" #8 Females of childbearing potential who do not agree to use reliable contraception or refrain from sexual activity for 24 hours following administration of flortaucipir injection will be excluded.
6. The risk language associated with ^{18}F-AV-1451 was changed. In the "less likely" section was changed to include nausea, lightheadedness/dizziness. In the "rare" section we added that "Some participants may experience atrial fibrillation and transient ischemic attack.

Revision 2, 10/29/2015

1. Removed the following people from the study team: Swapnil Bagade, Eric Byrum, Delphine Chen, Keith Fischer, Linga Reddy, Henry Royal, Kiran Sargar, Akash Sharma, Houman Sotoudeh, Marcus Raichle, Jerold Wallis, Spencer McFarlane.
2. Update scanner-related risks regarding skin tattoos with MRI.

Revision 1, 04/07/2015

1. Re-listed Spencer McFarlane from Study Coordinator to Additional Study Team Member. Kelley Jackson now listed as Study Coordinator.
2. Listed the following individuals on the protocol under Additional Study Team Member: Lisa Cash, Tony Durbin, Karl Friedrichsen, Russell Hornbeck, Christopher Owen, Betsy Thomas, Elizabeth Westerhaus
3. Added the following individuals as new Additional Study Team Members: Dr. Swapnil Bagade, Linda Becker, Dr. George Benzinger, Tyler Blazey, Dr. Eric Byrum, Dr. Delphine L. Chen, Dr. Farrokh Dehdashti, Dr. Keith C. Fischer, Dr. Nupur Ghoshal, Dr. Brian Gordon, Dr. Manu Goyal, Emily Gremminger, Nancy Hantler, Michael Harrod, Dr. Pamela LaMontagne, Dr. Parinaz Massoumzadeh, Dr. John C. Morris, Dr. Maria Ponisio, Dr. Jing Qi, Dr. Marcus E. Raichle, Dr. Henry D. Royal, Dr. Kiran Sargar, Dr. Joshua S. Shimony, Dr. Barbara Joy Snider, Dr. Houman Sotoudeh, Dr. Yi Su, Dr. Andrei Vlassenko, Dr. Jerold W. Wallis, Dr. Pamela Woodard.
4. Under Inclusion Criteria, specified that women of childbearing potential will have a *negative* urine pregnancy test 24 hours prior to *F 18 T807* drug administration.
5. We are now allowing for a non-physician designee to conduct participant assessment prior to T807 injection and prior to discharge from F 18 T807 imaging visit.
6. For Exclusion Criterion# 3, we have referenced a study-specific list of restricted medications.
7. The F 18 T807 PET acquisition protocol for the long scan has been revised such that we have the option of scanning for 105 continuous minutes, with a break of up to 15 minutes to be offered to the participant.
8. Clarified that a second CT attenuation scan may be conducted for the T807 long scan. In the event the participant needs to get off the scanner bed for a break, a second CT attenuation can be conducted.
9. Updated radiation risk statement, as related to the second CT attenuation scan (see #5 above).

10. Added statement that for those participating in the optional ^{18}F-FDG PET scan, participants must fast for 4 hours prior to ^{18}F-FDG injection. It is also clarified that prior to ^{18}F-FDG injection, a blood sample will be taken for glucose measurement.
11. We added option to do short FDG scan acquisition.
12. Vital signs will now be collected prior to F 18 T807 administration.
13. We will now be asking participants about history of traumatic brain injury using the Ohio State University Traumatic Brain Injury Identification (OSU TBI-ID) Method.
14. Clarified that women of childbearing potential who elect to undergo PET imaging with ^{18}F-FDG must have a negative urine pregnancy test no later than 4 days prior to the ^{18}F-FDG imaging session.
15. Description of MRI risks were updated to match wording in the other protocols under IND 123119.
16. Under 6.f. Scanner Procedures, Section (iv) was corrected to note that MR imaging may be conducted at the same time as the ^{18}F-FDG PET scan if conducted on the PET/MR scanner.
17. Revised neuropsychometric battery.
18. Updated Serious Adverse Event Reporting section to include reporting guidelines to Avid Radiopharmaceuticals/Eli Lilly.
19. Updated protocol version to Version 2 and protocol date to 04/07/2015.

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1. Overview

Tau aggregation and deposition in the form of neurofibrillary tangles is a major pathological hallmark of Alzheimer's disease (AD) pathology and is thought to represent a final common pathway for multiple neurodegenerative disorders, ranging from frontotemporal dementia, to Parkinsonism, to certain genetic forms of amyotrophic lateral sclerosis (ALS) [1-3]. In AD, where tau pathology has been best studied, postmortem studies demonstrate a progressive spreading, or staging, of tau pathology, beginning in the transentorhinal cortex, progressing through the temporal lobe and into the frontal and parietal lobes, and finally becoming diffuse [2, 4, 5]. It has been recently appreciated that tau deposition can be a significant pathological feature in some forms of familial ALS, and is especially prominent in cases caused by mutations in the *C9ORF72* gene. We have hypothesized that tau deposition may predict greater cognitive involvement and faster rates of disease progression. However, for all diseases with tau deposition, including AD and ALS, we have lacked the ability to stage the distribution and amount of tau pathology *in vivo*. In the last year however, new PET imaging tracers have been developed which are likely to revolutionize the field [6-8].

The optimum scanning and data analysis approaches, however, are still unclear. This project will collect quantitative pilot data that will allow the characterization of uptake and binding of ^{18}F-AV-1451 (also known as F 18 T807, also known as 7-(6-fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole), a novel tau imaging compound, in individuals with and without brain tau fibrils. The primary goal of this study is to develop this highly promising tau imaging technique as an antecedent biomarker of neuronal cell loss, regardless of whether that loss leads to cognitive decline (as in AD) or to weakness and fronto-temporal dementia (as in ALS). That is, we propose to obtain preliminary data that will support the possibility of detecting cognitive decline or neuronal loss in its earliest stages, **before** the occurrence of dementia or the onset of weakness. Preliminary data generated from this study will be used for submission of National Institutes of Health (NIH) grants investigating neurodegenerative disorders that include, but are not exclusive to, AD, ALS, frontotemporal dementia (FTD), Parkinson disease, and HIV-Associated Neurocognitive Disorders (HAND).

Under this study protocol, collaborating neuromuscular physicians will refer participants for MR and PET imaging to evaluate tau distribution in the brain of subjects with ALS, or ALS with frontotemporal dementia caused by different genetic mutations, or any mutation carrier (with or without symptoms), or normal controls.

We hypothesize that *in vivo* tau imaging will ultimately:

- Demonstrate the presence of tau fibrils in the brain of subjects with ALS or ALS with fronto-temporal dementia, especially in those with mutations in *C9ORF72,* and may discriminate between ALS causes by *C9ORF72* and mutations in other genes.
- Demonstrate that cortical F 18 T807 uptake correlates with markers of ALS disease severity, degrees of cognitive impairment, and rates of decline.
- Demonstrate correlations between F 18 T807 uptake with CSF markers of tau, including tau and p-tau.
- Co-localize with specific cognitive deficits (i.e. patients with tau deposition in the left lateral temporal lobe will have primarily language deficits).

2. Objectives

To begin to explore these hypotheses, we will pursue the following specific aims (SA).

SA1: Perform human *in vivo* tau imaging using F 18 T807 in 20 participants age 18 and older. Participants will have biomarker imaging and CSF assessments, and clinical and psychometric assessments.

SA2: Develop quantitative analysis methods for F 18 T807 PET scans.

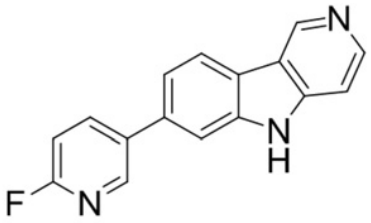
Exploratory SA3: Correlate regional quantitative T807 binding potentials (BPs) with (a) presence and progression of cognitive impairment and weakness, as documented by clinical psychometric and strength testing, with (b) brain atrophy by volumetric MRI, (c) CSF and amyloid imaging markers of AD pathology, (d) performance on psychometric tests, (e) clinical diagnosis, and, if the participant expires, (f) autopsy findings.

3. Background Information

C9ORF72-associated disease:

A hexanucleotide repeat expansion in an intron of the *C9ORF72* gene was recently identified as the most common cause of two fatal diseases characterized by progressive neuronal degeneration- amyotrophic lateral sclerosis (ALS) and fronto-temporal dementia (FTD)[9]. Early pathological studies in *C9ORF72* repeat expansion carriers highlighted the prevalence of cytoplasmic TDP-43 and p62 aggregate pathology[10, 11]. As the toxic-RNA mechanisms have been uncovered, more pathognomonic findings have also been found, including nuclear RNA foci and cytoplasmic aggregates of RANT-generated dipeptides[12]. In our early clinic-

pathologocial studies of *C9ORF72* carriers, we uncovered a subset of patients whose neurons demonstrated significant accumulation of intracellular tau fibrils[13]. Subsequent publications have confirmed that in some cases, the burden of tau neurofibrillary tangles (NFTs) is sufficient to meet criteria for Alzheimer's disease (AD). The burden of tau pathology in *C9ORF72* disease has been found to be equivalent to that observed in other forms of frontotemporal dementia and high levels of tau and phosphorylated tau have been observed in CSF from patients with *C9ORF72* expansions[14, 15]. These data highlight a potential role for tau pathology in *C9ORF72*-associated neurodegeneration. As in other neurodegenerative diseases with tau pathology, tau aggregation could exacerbate *C9ORF72*-specific mechanisms of degeneration[16]. We hypothesize that the degree and distribution of cortical tau pathology in *C9ORF72* expansion carriers will correlate with the likelihood of cognitive dysfunction and with faster rates of disease progression. We propose leveraging a novel tau imaging tracer available here at Washington University to obtain pilot data addressing this novel hypothesis and to explore the cortical tau burden as a potential biomarker in *C9ORF72* diseases.



T807

Figure 1: Chemical structure of T807

^{18}F-AV-1451 (also known as F 18 T807, also known as 7-(6-fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole) is a novel *in vivo* human tau PET imaging agent [6, 17]. It was initially developed through screening of human AD brain sections, combining autoradiography and immunostaining, and has undergoing initial human studies including toxicology and radiation dosimetry. Preliminary results suggest it can stage tau pathology in a manner similar to Braak and Braak staging.

4. Statement of Qualifications

The FDA 1572 Form is provided in the IND submission (see Appendix II) along with curriculum vitae (see Appendix III) for the study's Principal Investigator, Tammie L.S. Benzinger, M.D., Ph.D., Washington University School of Medicine, St. Louis, Missouri.

5. Inclusion/Exclusion Criteria

All participants will be evaluated for the following:

Inclusion Criteria

1. Male or female participants, at least 18 years of age.
2. Clinically diagnosed with amyotrophic lateral sclerosis (ALS), fronto-temporal dementia (FTD), or both; or a carrier of a mutation known to cause ALS or FTD (with or without symptoms); or a normal control.
3. Participant is able and willing to undergo testing (psychometric testing, MRI or CT, PET, radioactive tracer injection; for those unable to undergo an MRI, CT will be used to generate regions-of-interest).
4. Females of childbearing potential without documented history of menopause or hysterectomy who do participate must not be pregnant or breastfeeding at screening (negative urine β-HCG within 24 hours prior to injection of radioactivity), and must agree to avoid becoming pregnant.

Exclusion Criteria

1. Has any condition that, in the Investigator's opinion, could increase risk to the participant, limit the participant's ability to tolerate the experimental procedures, or interfere with the collection/analysis of the data (for example, participants with significant respiratory involvement may not be able to lie flat during the scanning procedures).
2. Is deemed likely unable to perform the imaging procedures for any reason.
3. Has a high risk for Torsades de Pointes or is taking medications known to prolong or may prolong QT interval (refer to study's list of restricted medications).
4. Has hypersensitivity to F 18 T807 or any of its excipients.

5. Contraindications to PET, PET-CT or MR (e.g. electronic medical devices, inability to lie still for long periods) that make it unsafe for the individual to participate.
6. Severe claustrophobia.
7. Currently pregnant or breast-feeding.
8. Females of childbearing potential who do not agree to use reliable contraception or refrain from sexual activity for 24 hours following the administration of flortaucipir injection will be excluded.

6. Methods

a. Study Design

A single-center, open-label baseline controlled imaging study designed to assess whether brain tau fibril uptake of F 18 T807 as measured by PET correlates with cognitive and clinical status of individuals with and without brain tau fibrils.

b. Participant Population

Twenty (20) participants over a period of approximately 5 years will be enrolled. Participants will undergo an F 18 T807 scan at the Center for Clinical Imaging Research (CCIR) at Washington University using an adaption of the protocol developed by Kolb and colleagues [6]. An MRI will be conducted. (For those unable to undergo an MRI, CT will be used to generate regions-of-interest.) Participants will be asked about their medical history, family history, surgical history, and current medications. We will evaluate history of traumatic brain injury using the Ohio State University Traumatic Brain Injury Identification (OSU TBI-ID) Method. This will take approximately 10 minutes. Additionally, participants will be invited to undergo the following assessments:

i) PET imaging with fludeoxyglucose (18F-FDG), for measurement of the cerebral metabolic rate of glucose consumption.
ii) A physical examination (if one has not been conducted under IRB ID# 201312111).

c. Recruitment

Participants will be referred to an imaging research coordinator on the Principal Investigator's study team. The research coordinator will discuss the study with the participant over the phone and conduct a pre-screening assessment. The research coordinator will have access to the health history data collected by the referring physician at the participant's most recent assessment. The research coordinator will review the

participant's general health information with the participant to assess any contraindications to PET or MR imaging. If the participant appears to be eligible, they will be given a consent form to read, review, and discuss with others who may be able to help them make a decision about participating in the study. Study staff will provide adequate time for the participant to ask questions to ensure that any concerns are addressed prior to study enrollment.

d. Imaging Study Procedures

i) F 18 T807 Imaging

Participants will undergo a PET scan using the tau-imaging tracer, F 18 T807. Participants will come to the imaging center and will have a catheter placed for intravenous (i.v.) administration of F 18 T807. Participants will receive a single 6.5-10 mCi intravenous bolus of F 18 T807 infused over 20 seconds. Participants may also undergo up to two low dose CT scans for attenuation correction.

There are two acceptable procedures for obtaining the F 18 T807 PET scans:

1) In the preferred approach, participants will receive a single IV bolus injection of approximately (240-370 MBq) 6.5-10 mCi of F 18 T807, followed by a saline flush. Scanning will start at the same time as the injection and continue for a total of 105 minutes. If needed, the participant may take up to a 15-minute break after the first 60 minutes of scanning, and scanning should resume immediately after the break. For the 60 minutes, PET data will be acquired in 3-dimensional list mode and will be binned into 38 dynamic frames (10 frames × 6 s, 6 frames × 20 s, 4 frames × 30 s, 5 frames × 60 s, 5 frames × 120 s, 8 frames × 300 s). After the break, the PET data will be acquired in 5-minute frames and will be summed into one static frame. This imaging visit will take approximately two hours.
2) For those who cannot tolerate the full exam, participants will receive a single IV bolus injection of approximately (240-370 MBq) 6.5-10 mCi of F 18 T807, followed by a saline flush. Participants will rest quietly in an uptake room following the injection. At approximately 75 minutes following injection, a continuous 30 minute brain scan (6 acquisitions of 5 minute duration) will be performed. This imaging visit will take approximately two hours.

The following safety assessments will be performed at the time of the F 18 T807 PET imaging session:

1) A physician, or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse, or a regional equivalent) designated by the Principal Investigator, must assess or evaluate the participant prior to administration of F 18 T807 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 attention;
2) For women of childbearing potential, a negative urine pregnancy test must be obtained up to 24 hours prior to F 18 T807 dose administration;
3) Vital signs will be taken prior to F 18 T807 dose administration;
4) The injection site will be observed for evidence of inflammation or damage to the surrounding tissue where the dose was injected;
5) The participant will be requested to void after completion of the PET scan;
6) Adverse events (AEs) will be continuously monitored during the F 18 T807 imaging session; participants who experience an AE will not be discharged from the imaging center until the event has resolved or stabilized; and
7) A physician, or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse, or a regional equivalent) designated by the Principal Investigator, will 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 attention.

A follow-up phone call to the participant will be conducted within 2 or 3 business days of the F 18 T807 imaging visit, but not before 48 hours post-injection, to confirm participant well-being and to collect information about any new adverse events.

ii) MR Imaging

Participants will be asked to undergo an MRI scan. (For those unable to undergo an MRI, CT will be used to generate regions-of-interest.) MR imaging will be formed using the established Washington University protocols for dementia imaging. These include T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence (1 mm isotropic voxels). This scan will take approximately one hour.

iii) ^{18}F-FDG Imaging (Optional)

Participants will be invited to undergo an optional ^{18}F-FDG PET scan. ^{18}F-FDG uptake and trapping may be used to image the cerebral metabolic rate of glucose consumption

(CMRGlc). Participants will be asked to fast for 4 hours prior to injection of ^{18}F-FDG. Women of childbearing potential must have a urine pregnancy test no later than 4 days prior to ^{18}F-FDG dose administration. Prior to the ^{18}F-FDG PET scan, an antecubital intravenous catheter will be placed in the arm for tracer injection and blood sampling for glucose levels. Blood sampling will be done once prior to FDG tracer injection. Measurements of CMRGlc will be performed after slow intravenous injection of 5 mCi of 18F-FDG. Dynamic acquisition of PET emission data will continue for 60 minutes according to the following scheme: 25 x 5 sec frames, 9 x 20 sec frames, 10 x 60 sec frames, 9 x 300 sec frames. All data will be corrected for head motion that occurs during the ^{18}F-FDG scan. This scan will take approximately one hour. For those unable to tolerate a full 60-minute dynamic scan, a 30 minute scan may be conducted 30 minutes after ^{18}F-FDG administration.

e. Participant Preparation

Participants will be asked to arrive at the Center for Clinical Imaging Research (CCIR) located on the 10th floor of Barnes-Jewish Hospital at Washington University School of Medicine. The location allows outpatients and inpatients to undergo research-related imaging protocols in a safe imaging environment. The CCIR facility has complete clinical monitoring and resuscitation equipment including a fully supplied adult "crash cart" with a defibrillator as well as shielded patient uptake rooms with a television and warm blankets for patient comfort.

A PET-certified registered nurse or CCIR PET technologist will administer radiopharmaceuticals.

For women of child-bearing potential, a urine pregnancy test will be conducted in the CCIR prior to the imaging procedures. Women who are pregnant or breast-feeding will not be eligible to participate in the study.

f. Scanner Procedures

The preferred scanner for F 18 T807 imaging is the PET/MR; however, in the event that there are technical difficulties or scanner availability issues, there will be the option to conduct the scans on any of the following scanners:

i) On the Siemens model ECAT HRplus 962 PET scanner (stand-alone PET scanner) (located in Barnes-Jewish Hospital, West Pavilion, Neurology and Neurosurgery Intensive Care Unit (NNICU) Suite 10400) for the PET scans: A NeuroShield

(Scanwell Systems) will be used to reduce random and scattered coincidences originating from extracranial radioactivity. A softened thermoplastic mask with enlarged eyeholes will be placed over the head and secured. After hardening, the mask will help minimize head motion. The participant will be positioned in the scanner such that the cantho-meatal line is approximately 1.0 cm above, and parallel to, the lowest imaging plane. A transmission scan will be obtained to correct attenuation. The participant will be asked to close their eyes. The room will be darkened and all noise minimized. A 5-10 minute transmission scan will be obtained for attenuation correction. The subject will rest with eyes closed during the scan.

ii) On the Siemens Biograph 40 PET/CT scanner (located in the Center for Clinical Imaging Research (CCIR), Barnes-Jewish Hospital, West Pavilion) for the PET scans: A softened thermoplastic mask with enlarged eyeholes will be placed over the head and secured. After hardening, the mask will help minimize head motion. The subject will be positioned in the PET scanner such that the cantho-meatal line is approximately 1.0 cm above, and parallel to, the lowest imaging plane. A three-second X-ray Topogram will be acquired in the lateral plane to visualize the head and determine the exact scan position. Prior to the PET scan, a spiral CT (Computed Tomography) scan will be performed for attenuation correction at the low dose CT setting of 37.5 mAs (which is 25 effective mAs). For the T807 scanning protocol Option 1 (PET acquisition from 0-105 minutes with option for break after the first 60 minutes), a second CT may be acquired after the break, if a break is taken. To minimize any possible variations in regional blood flow and initial tracer uptake, the subject will be asked to close their eyes. The subject will rest with eyes closed during the scan.

For purposes of attenuation correction CT scanning and in accordance with FDA recommendations released July 2009, participants will be questioned by the PI or PI's designee before scanning about implanted medical devices or pumps. The MRI screening form includes the question "Do you wear or have an implantable medical device such as a pacemaker or a drug pump? ☐Yes ☐No". This questionnaire will be signed and dated by the participant and kept in the participant's study records. In addition, the topogram will be checked prior to start of the CT attenuation scan. If the participant has an implanted medical device or medicine pump, the participant will be advised about possible malfunction of such devices that could possibly be related to the attenuation CT scan. It will be emphasized that this is a rare occurrence. As with any

research protocol the subject will make the final decision whether or not to participate after appropriate discussion with family/friends as desired.

iii) On the Siemens mMR PET/MR scanner (located in the Center for Clinical Imaging Research (CCIR), Barnes-Jewish Hospital, West Pavilion) for PET scans: A softened thermoplastic mask with enlarged eyeholes may be placed over the head and secured. After hardening, the mask will help minimize head motion. The subject will be positioned in the scanner bed such that the cantho-meatal line is approximately 1.0 cm above, and parallel to, the lowest imaging plane. A three-second X-ray Topogram will be acquired in the lateral plane to visualize the head and determine the exact scan position. A brief (less than 1 minute) CT scan may also be conducted on the PET/CT scanner for attenuation correction.

iv) On the Siemens mMR PET/MR scanner (located in the Center for Clinical Imaging Research (CCIR), Barnes-Jewish Hospital, West Pavilion) for the MRI scan: The MR system is a 3.0T whole body MRI system. All basic sequences and many sequences in development are compatible with this system. Features include: 60 cm system bore/50 field of view and an integrated MR gradient coil. Maximum amplitude for all three gradient axes is 45 mT/m and slew rate is 200 T/m/s. Standard PET-compatible Tim® (Total imaging matrix) head and body phased array coils compatible with the Siemens Verio are available for use. The MRI scan may be conducted simultaneously as the ^{18}F-FDG PET scan.

v) On the Siemens Trio 3 Tesla scanner (located in the Center for Clinical Imaging Research (CCIR), Barnes-Jewish Hospital, West Pavilion) for the MRI scan. The MR system is a 3.0T whole body MRI system. All basic sequences and many sequences in development are compatible with this system.

vi) On the Siemens MAGNETOM Skyra 3 Tesla scanner (located in the Center for Advanced Medicine (CAM), Barnes-Jewish Hospital, West Pavilion) for the MRI scan. The MR system is a 3.0T whole body MRI system. All basic sequences and many sequences in development are compatible with this system.

g. Neuropsychometric Assessments

Participants will undergo cognitive and psychological assessments. This will take approximately 2 hours to complete. The following assessments will be conducted:

i) Hopkins Verbal Learning Test
ii) Trailmaking Parts A and B
iii) Digit-Symbol Substitution Task
iv) Letter-Number sequencing
v) Wisconsin Card Sorting Test – 64 card version
vi) FAS Test
vii) Category Fluency
viii) Action Fluency
ix) Stroop Interference Test
x) Brief Visuospatial Memory Test – Revised
xi) Boston Naming Test
xii) Mini Mental Status Examination
xiii) Digit Span
xiv) Continuous Performance Task
xv) Montreal Cognitive Assessment
xvi) Frontal Systems Behavior Scale
xvii) Logical Memory Test
xviii) Ohio State University Traumatic Brain Injury Identification Method

h. Follow-up

A follow-up phone call to the participant will be conducted within 2 or 3 business days of the F 18 T807 imaging visit, but not before 48 hours post-injection, to confirm participant well-being and to collect information about any new adverse events.

i. Analytic Plan

The primary goal of this study is to perform and analyze F 18 T807 tau PET imaging in a well-characterized human cohort. Data generated by this pilot study will be used to generate power calculations, aims, and hypotheses for NIH grant applications. Because of the novel nature of this project, a power calculation cannot be performed at this time. We will collaborate with the Knight ADRC Biostatistics Core to conduct extensive exploratory analyses to generate novel hypotheses for future testing. For example, we will correlate each imaging modality (MRI volumetrics, PET amyloid imaging, F 18 T807 PET imaging) from each matched FreeSurfer region, and locate the combinations of modalities and regions that best correlate with cognitive performance.

7. Informed Consent

All participants will undergo written informed consent prior to any study procedures. Participants are interviewed over the phone to determine their eligibility (with a pre-screening assessment) and interest in participation. Participants that appear to meet the entrance criteria are given a more detailed explanation of the protocol's procedures including a description of the protocol, the risks along with procedures to minimize these risks and the participants' rights and responsibilities. The participants will be mailed or given a copy of the informed consent so that they can discuss participation with their private physician or family. If the participant wishes to participate, the informed consent is signed prior to imaging procedures. Participants are specifically told that they may withdraw consent for participation at any time without adversely affecting their medical care.

Participants will be reimbursed for their participation in the imaging studies. Participants will be asked to provide their social security number (SSN) in order for us to reimburse them. Participants will be advised that they may choose to participate without being reimbursed if they do not wish to provide their social security number (SSN) for this purpose. They will also need to provide their address because the reimbursement for their study participation will be mailed to them. Once a check is issued, it will take up to eight weeks for the check to arrive at the address the subject provided. If the participant's social security number is obtained for reimbursement purposes only, it will not be retained for research purposes.

8. Procedures for Maintaining Confidentiality

a. Data Security

All data obtained from research participation will be identified by a code number. All data will be kept in locked file cabinets and only made available to qualified research personnel.

b. De-identification of Data

Only code numbers will appear on any data and documents used for evaluation or statistical analysis. No Protected Health Information (PHI) will be shared with others. Publications emanating from this research will not identify individual patients. HIPAA compliance will be enforced as per Washington University policy and HRPO approval. Studies are done for research purposes only. No services are billed to Medicare or Insurance Companies. Reports from patients' records concerning research observations will not be available to outside medical facilities without the written consent of the subject.

De-identified study data will be maintained at Washington University. This de-identified data may also be shared with other investigators doing research in similar fields such as Alzheimer disease, other neurological disorders or related brain diseases and abnormalities. These investigators may be at Washington University or at other research institutions. This de-identified data may also be shared with large repositories for broad sharing with the research community. If the participant's research data is placed in one of these repositories, only qualified researchers who have received prior approval from individuals that monitor the use of the data, will be able to look at this information. This de-identified study data will also be shared with the U.S. Food and Drug Administration. Information from this research study has been or will be entered into a clinical trial databank that is maintained by the National Institutes of Health/National Library of Medicine. It will not include information that can identify the subject.

9. Assessment of Risks and Benefits

a. Risks

Potential risks are minimal as MRI and PET exclusion criteria and safety procedures will be applied. Participants with any metallic objects within their bodies will be screened using standard procedures at the Washington University Center for Clinical Imaging Research (CCIR) using criteria established and in place at Barnes-Jewish Hospital. For pre-menopausal women, a negative urine pregnancy test is required before radiopharmaceutical administration. Specific risks for each of the study procedures are listed below. The CCIR is a facility which provides both research and clinical imaging procedures. The facility operates in compliance with the safety guidelines for imaging and for privacy as directed by the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the Joint Commission on Accreditation of Healthcare Organization (JCAHO), the American College of Radiology (ACR), and the Nuclear Regulatory Commission (NRC). PET radiopharmaceuticals used in the CCIR are produced in compliance with United States Pharmacopeia (USP) Chapter 823 standards.

i) Intravenous (I.V.) Catheter Placement
(Likely) Participants may experience pain, bruising, and/or bleeding at the site of needle insertion for the intravenous catheter.

(Rare) There is a rare risk of infection from a needle insertion.

ii) Radiation
(Likely) This study will expose the participant to radiation from the F 18 T807 PET scan and from the CT of the head. The amount of radiation the participant will receive from one F 18 T807 scan, when averaged over the entire human body, is about 20% of the amount a person who works with radiation is allowed to have in one year. The risk from the radiation exposure in this study is too small to be measured. It is not a big risk when compared with other risks one takes every day (e.g., driving).

iii) Scanner Related Risks
(Less likely) Lying still in the scanner may produce some stiffness. Study staff will be nearby to stop the study in case the participant becomes uncomfortable and the exam will be terminated. (Rare) People with a fear of being in small, enclosed places may find this procedure uncomfortable. During the course of the exam, the technologists will be in communication with the participants and the study will be terminated if claustrophobia develops. If the participant undergoes an MR scan, the technician will inquire about possible metallic objects inside the participant's body. The MRI scanner produces a loud hammering noise. A pair of earplugs may be placed in the participant's ears to reduce the risk of hearing loss. Tattoos: There are certain risks associated with undergoing an MRI scan if one has a skin tattoo. These include risks associated with both cosmetic tattoos (eye-liner, lip-liner) and decorative tattoos. These risks are greater if the tattoo was not applied professionally, or if the ink used in the tattoo is iron-based. Associated risks include transient skin irritation, cutaneous swelling, or heating sensation. In rare instances patients with decorative tattoos have had a primary or secondary burn occur at the tattoo site. If the participant has a tattoo and decides to undergo the research MRI scan, we will offer the participant a cold, wet compress (washcloth) to put over the tattoo as a precautionary measure. This decreases but does not eliminate the risk. There is a rare risk of malfunction of worn or implanted electronic medical devices with CT scanning. The participant will be asked will be asked to advise the study investigator and research staff if he/she wears or has electronic medical devices

implanted such as a pacemaker or a drug pump. It has been reported to the FDA that CT scan may cause a malfunction of electronic medical devices.

iv) Risks associated with ^{18}F-AV-1451

Less Likely: Some participants are less likely to experience nausea, lightheadedness/dizziness, diarrhea, headache, and altered taste.
Rarely: Some participants may experience atrial fibrillation and transient ischemic attack**.** All reported events were mild in intensity and all subjects recovered from these events. Since ^{18}F-AV-1451 is a new compound that is being studied in clinical trials, you may experience side effects that we do not know about yet.

v) Risks from Additional Study Procedures

^{18}F- FDG (Optional)

(Likely) This study will expose the participant to radiation from the^{18}F-FDG PET scan and from the CT of the head. The amount of radiation the participant will receive from one ^{18}F-FDG PET scan, when averaged over the entire human body, is about 6% of the amount a person who works with radiation is allowed to have in one year. The risk from the radiation exposure in this study is too small to be measured. It is not a big risk when compared with other risks one takes every day (e.g., driving).

vi) Questionnaires

Participants may experience emotional discomfort when answering some questions in the questionnaires (i.e. MRI and PET safety screening records; neuropsychometric assessment). If any particular question makes the participant uncomfortable, the participant may discuss its importance and the need to answer it with the specially-trained interviewer. Participants have the right to refuse to answer any question for any reason. If safety screening cannot be completed, then the imaging exams will be cancelled. Participants may experience fatigue or embarrassment from the exercises of memory, movement, and attention.

vii) Other Risks

Participants may experience all or some of the risks listed above. There may also be unknown risks. The PI will answer any questions the participant has about these risks. For participants who find the scanning session unpleasant, the session will be immediately terminated.

b. Alternative Procedures

If the participant is unable to undergo PET imaging with F 18 T807, there are no alternative procedures.

10. Benefits

Taking part in this research study will not benefit the subject directly. An indirect benefit is contributing to biomedical research. A possible benefit to society from this research is a better understanding of ALS that may eventually lead to improvements in medical care.

11. Regulatory and Reporting Requirements

a. Regulatory Compliance

The Principal Investigator will conduct the protocol in adherence to institutional guidelines and in adherence with the Federal Food and Drug Administration (FDA), Department of Health and Human Services (DHHS), and the Code of Federal Regulations (CFR) procedures and requirements governing the use of investigational new drugs and the monitoring of serious adverse events (21 CFR 312).

b. Adverse Events Monitoring and Documentation

Each participant will be monitored for adverse events (AEs). All AEs will be recorded. The severity/intensity of the AE and its relationship to the administration of the study drug, F 18

T807, will be made by the Principal Investigator. Adverse events for purposes of this imaging trial are defined as any untoward medical occurrence in a subject who receives F 18 T807. The event does not necessarily have to be causally related to F 18 T807 to qualify as an adverse event. An adverse event can be any unfavorable or unintended sign, symptom or disease temporally associated with the injection of F 18 T807, whether or not it is considered related to F 18 T807. Signs and symptoms that are believed to be due to pre-existing condition (started prior to dose of study medication) will not be recorded, unless there is an increase in frequency or severity.

For the purposes of this study, untoward medical occurrences will be considered associated with the use of F 18 T807, and thus reported as adverse events, if they occur within 48 hours after F 18 T807 administration. Adverse experiences that occur after administration but outside the 48 hour reporting window will not be reported unless the investigator believes they are attributable to the drug.

In order to capture possible adverse effects of trial participation, trial-emergent adverse events will also be recorded as an untoward medical occurrences occurring during the trial period but not during the 48 hour window following the administration of F 18 T807. The trial period will be defined as beginning with the signing of consent and ending 48 hours after the last study procedure, including (but not limited to) MR imaging, FDG PET scan, florbetapir F 18 PET scan, and lumbar puncture.

Intensity/severity of an AE will classified as: (1) *Mild:* A mild adverse event is an adverse event, usually transient in nature and generally not interfering with normal activities; or (2) *Moderate:* A moderate adverse event is an adverse event that is sufficiently discomforting to interfere with normal activities; or (3) *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.

c. Serious Adverse Event (SAE)

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

- Death;
- Initial or prolonged inpatient hospitalization;
- 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.

d. Reporting of Serious Adverse Events

1. To Washington University's Institutional Review Board:

Within 24 hours of becoming aware of a serious adverse event (SAE), the study team will report the SAE to Washington University's Institutional Review Board, the Human Research Protection Office (HRPO). Serious adverse events must be serious, unexpected, and reasonably related to the research. Events which do not meet the requirements for SAE reporting will be reviewed by the Principal Investigator and documentation of the fact that the event does not meet SAE reporting requirements will be maintained in the participant's chart.

Serious adverse events occurring after a participant receives 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 will not be recorded unless the investigator feels the events were related to the investigational product or a protocol procedure.

If a participant 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 will not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

2. To the U.S. Food and Drug Administration:

The Sponsor-Investigator of this IND will comply with the FDA regulations as well as Title 21 of the Code of Federal Regulations, by adhering to the following:

i) Report any unexpected fatal or life-threatening suspected adverse reactions to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]. All 7-day reports will be submitted by telephone or fax.

ii) Report any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to the FDA and to all sub-investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. All 15-day reports will be submitted in paper format.

iii) All documentation will be included in the IND Annual Report. Modifications to the informed consent will be made if deemed necessary. Submitting annual progress reports within 60 days of the anniversary of the date that the Exploratory IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

iv) Reporting to the FDA. All reports will be submitted to the FDA at the following address:

Division of Medical Imaging Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

3. To Avid Radiopharmaceuticals/Eli Lilly:

Because the IND under which this study is conducted (IND 123,119) cross-references Avid Radiopharmaceutical's IND 119,863, the study team shall notify Avid/Eli Lilly within twenty-four (24) hours of receiving notification of any serious adverse event experienced by a patient participating in the Study and receiving F 18 T807. For purposes of this requirement, "serious" means: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; Johor (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events may be reported via one of the following:

i) Fax: 317-453-3402

ii) Toll-free fax: 866-644-1697

iii) MAILINDATA_GSMTINDY@LILLY.COM

e. Data Safety Monitoring (DSM) Reporting

Safety data will be reviewed by the Principal Investigator and the research team as the information becomes available. An annual report will be submitted to Washington University's Institutional Review Board (IRB). This report will include the protocol title, IRB protocol number, the number of participants enrolled to date, statement of about study status, description of problems, description of any significant changes to the study design (previously approved by the IRB), and any participant experiences. All pertinent information will be provided in the FDA Annual Report.

f. Protocol Deviations

All efforts will be made to follow the protocol as specified above. In the event a situation occurs which requires deviation from this protocol, (i.e., less than expected tracer production, problems with the scanner, participants unable to tolerate imaging) the Principal Investigator will have final authority over whether or not a study is prematurely completed. All protocol deviations will be documented and maintained in the participant's research chart. Deviations such as less than expected tracer production can be accounted for during data analysis and will not necessarily result in cancellation of the scan. In the event of any deviations from the investigational plan that affects the life or physical well-being of a participant in any emergency, the Investigator will notify the IRB. Such notice will be submitted as soon as possible, but in no event later than 5 working days after the emergency occurred, except in such an emergency where prior approval by the sponsor-investigator is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human rights, safety, or welfare of human subjects. In this case, the FDA and IRB will be notified as required per the sponsor/investigator responsibilities outlined in 21 CFR 312.

12. Case Report Forms

Case Report Forms (CRFs) will be used to document eligibility criteria, demographic information, pregnancy test results, administration of radiopharmaceuticals, imaging visit sessions, telephone contact 2-3 days post-T807 injection, adverse events and serious adverse events, and record of contact with participants.

13. Record Archives

As set forth by 21 CFR 312.57, records and reports will be retained for 2 years after a marketing application is approved for the drug; or if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has so been notified.

14. REFERENCES

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