NCT02676843

Study Title: Tau PET imaging with 18F-AV-1451 in subjects with MAPT mutations
IRB Protocol Number: AAAP4551
Version: 07/24/2015

Principal Investigator: Edward Huey, MD
Co-Investigator: William Kreisl, MD
Study Coordinator: Masood Manoochehri

PROTOCOL SUMMARY

Research question(s):
A novel PET tracer (18F-AV-1451) designed to measure the amount of tau protein in the brain will detect abnormal accumulations of tau in the brains of patients with tau mutations, but not their unaffected relatives.

Scientific abstract:
Objective: To determine the ability of a new PET tracer that binds to tau, 18F-AV-1451, to detect tau in subjects with and without mutations in the MAPT gene the codes for the protein tau.
Study Population: Control subjects without MAPT mutations, presymptomatic mutation carriers, and symptomatic mutation carriers.

Outcome measures:
The primary outcome measure will be a qualitative assessment of tau deposition on the 18FAV-1451 scans

Lay abstract:
We will be testing the ability of a new PET tracer, 18F-AV-1451, to detect depositions of a protein, called tau, in the brains of people with a mutation in the tau gene that causes deposition of the protein and in people without the mutation.

Subject Selection
Patients will be recruited from existing studies and from patients seen in the Columbia memory disorders clinic.

Inclusion criteria: Members of families with established MAPT mutations, who either have the capacity to consent to participate in the protocol, or else have designated a surrogate/proxy to consent to participate in this study.

Exclusion criteria: Unwillingness to participate and/or on a medication which significantly prolongs QT interval.

Safeguards for Vulnerable Populations
The proposed study, including the potential risks and benefits, will be discussed with the potential subjects, and they will be given copies of the consent form to read. Decision-making capacity to provide informed consent, including understanding the purpose of the study and the risks and benefits of participating, will be assessed by the evaluating physician and documented in the chart. Individuals with intact decision-making capacity will sign the consent form. We expect the majority of subjects to have capacity to provide informed consent.
All subjects with impaired capacity to provide informed consent will be evaluated by the physician for their ability to assign a surrogate. Subjects who demonstrate capacity to assign a surrogate will identify a surrogate for the remainder of the study. Surrogates permitted are

designated family members (only patient, spouse, or adult child), or may be another individual chosen by Patient Chosen Surrogate (PCS) method. The study will be explained to each potential subject and surrogate, and written informed consent must be obtained from the surrogate. If the participant does not have the capacity to assign a surrogate, he or she will not be allowed to participate in the study. The consent process will be repeated at each evaluation, and the above procedures will be followed for any individual that loses capacity during the course of the study. Subjects will not be given diagnoses as part of their participation in this protocol. Some may be symptomatic and have received a diagnosis and others may be presymptomatic and had genetic testing and know their status. This knowledge will not preclude their participation in the study, but diagnosis and genetic information will not be given to subjects through their participation in this study.

Study Purpose and Rationale

We will examine tau deposition in patients with MAPT mutations and their family members using a new PET tracer, 18F-AV-1451. MAPT mutations cause Frontotemporal dementia (FTD). We have an opportunity to examine the tau deposition in genetic FTD by obtaining 18F-AV-1451 tau tracer imaging on symptomatic, pre-symptomatic, and non-carrier subjects in families with MAPT mutations. This will achieve the following important aims: 1. Elucidate the early course of genetic FTD due to tau. When does tau start to be laid down? What are the earliest brain regions affected? 2. Validate the 18F-AV-1451 tau tracer by demonstrating its ability to distinguish MAPT mutation carriers from non-carriers.

Study Design and Statistical Procedures

This is an initial proof of concept study. As such, we will qualitatively examine each scan for tau positivity and not perform quantitative statistical analyses.

Study Procedures

We propose to perform 18F-AV-1451 scanning on 16 subjects from families with known tau mutations over 2 years (8 per year) including 6 controls, 5 presymptomatic mutation carriers, and 5 symptomatic mutation carriers. The controls will be non-mutation carrying members of families in which some family members have MAPT mutations. Pregnant women will be excluded from the study. The tracer will be manufactured at Avid Radiopharmaceuticals in Philadelphia, PA and transported to Columbia University Medical Center by courier for administration. See (Zhang et al., 2012) for details of 18F-AV-1451 synthesis and quality control. Adverse events will be monitored continuously during the imaging session. Subjects who experience any adverse event during an imaging session will not be discharged until the event has resolved or stabilized.

Study Drug

18F-AV-1451, also known as [18F] T807, is a tracer that was developed by Avid Radiopharmaceuticals, a company later acquired by Lilly, to image tau protein in humans in vivo. It has shown suitable tau affinity, target selectivity, and pharmacokinetic characteristics for tau imaging (see below) (Zhang et al., 2012). The developers of 18F-AV-1451 have reviewed the effects of the 10 +14 C>T mutation observed in our family and the mutation should not interfere with 18F-AV-1451 binding to tau in the 10 +14 C>T mutation carriers. We have successfully

applied to Avid radiopharmaceuticals for the use of 18F-AV-1451 and they have approved us to use 18F-AV-1451 for investigation and are providing us the tracer for free.
Autoradiography studies have demonstrated that 18F-AV-1451 binds with high affinity to tau positive brain sections from AD patients, whereas minimal to no binding was observed in tau negative, amyloid positive samples or in tau negative and amyloid negative control groups (Chien et al., 2013). The correlation of 18F-AV-1451 in these autoradiography studies was high ($r^2=0.9036$) for paired helical filament-tau (PHF-tau, the aggregated fibrillary form) and low for -amyloid ($r^2=0.0827$). The Kd calculated for 18F-AV-1451 binding to tau protein in human brain slices was measured to be approximately 15 nM. Subsequently, the Kd calculated for 18F-AV-1451 binding to PHF-tau purified from the human brain samples was measured at 0.7 nM. In vivo animal kinetic studies were supportive of further development as 18F-AV-1451 demonstrated rapid uptake in mouse, rat, and monkey brain followed by moderate clearance (Zhang et al., 2012; Chien et al., 2013). 18F-AV-1451 is being used for research purposes and will be handled in accordance with the CUMC Research Pharmacy procedures and NYP policy P168, Version 4. Effective date: August 24, 2009 34 Investigational Drugs: Use and Control.

Study Subjects
We propose to perform 18F-AV-1451 scanning on 16 subjects over 2 years (8 per year) including 6 controls, 5 presymptomatic mutation carriers, and 5 symptomatic mutation carriers.

Recruitment
Subjects who previously participated in a previous protocol at Columbia will be recruited for this study. These subjects already have an existing relationship with the PI. Subjects participating in that protocol who meet the inclusion, but not the exclusion, criteria of this study will be told about the study and given the contact information of this study team by Dr. Huey.

Participants will also be recruited from patients seen at the Columbia Memory Disorders Clinic. The physicians at this clinic will be informed of this study so that if they identify a potential subject for this study, they can give that patient our contact information for potential participation in this study.

Informed Consent Process
We will obtain informed consent prior to any procedures. Only subjects with capacity to provide their own consent may consent or subjects who have a legally-authorized representative or guardian or a designated health care proxy that does not exclude research may consent on behalf of the subject to participate in this study. The study will be explained to each prospective patient or representative, and written informed consent must be obtained from the patient or representative before the patient participates in any study-related procedures.

Confidentiality of Study Data
Each participant's identity and participation in this study will be kept confidential in our database. All records will be stored in a computer file and access will be restricted to research staff. All questionnaires and other forms generated from the data collection will be kept in locked file cabinets, and only the investigators will have access to this information. Participant names will not be used. Rather, we will assign a code number that will be associated with all

information collected. Information presented or published for scientific purposes will not include participant names.

Privacy Protections
Research records are maintained in locked paper files and secured computer files, available only to research staff and institutional personnel as part of routine audits. Information is coded and password protected. Access is restricted to the authorized scientific investigators.

Identity of participants will not be shared with any investigators. Data that has been stripped of all identifying information from genetic analysis will be kept separate from the clinical and demographic data stored at the Taub Institute and can only be accessed by authorized individuals.

Potential Risks
Preclinical toxicity studies of 18F-AV-1451 (i.e. using non-radioactive 18F-AV-1451) showed a good safety profile with no observable effects at high multiples of the intended maximum human dose (Chien et al., 2013). The initial exploratory investigations of 18F-AV-1451 have been performed as part of two studies in older human subjects with a low probability of AD, in older subjects with a high probability of AD and in middle aged and young control subjects.

The objectives of the two studies were to establish the preliminary safety of 18F-AV-1451 and to assess the feasibility of 18F-AV-1451 as a potential PET biomarker for imaging pathological tau in human brains. As of the cutoff date of 19 September 2013, a total of 18 subjects have been enrolled in these studies (unpublished data from Avid Radiopharmaceuticals). Each subject received one intravenous bolus dose of approximately 10 mCi (370 MBq) of 18F-AV-1451. 18F-AV-1451 was well-tolerated; three subjects reported adverse events that were mild in severity and not considered related to study drug administration (two subjects reported headache, one subject reported diarrhea).

No consistent or clinically significant changes in vital signs, laboratory, and ECG values were observed in a completed analysis of 11 subjects. Preliminary human dosimetry results for 18F-AV-1451 have been computed for 3 subjects. The results showed both hepatobiliary and, to a smaller extent, 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 18F-AV-1451 was calculated to be 9.18 mSv (unpublished data from Avid Radiopharmaceuticals).

Data and Safety Monitoring
We will not have a specific Data and Safety Monitoring Board. Adverse events will be documented in the patient's chart. As far as possible, each adverse event will be described in the following manner and tabulated: 1) duration; 2) severity grade (i.e. mild, moderate, serious); 3) relationship to study; and 4) actions taken by the investigators. Unexpected and serious adverse events will be reported to the IRB within 2 days for death or life threatening events, and within 15 days for all others. We will also report all adverse events to Avid Radiopharmaceuticals who is monitoring safety data for this compound.

We will ensure proper monitoring per FDA and IRB guidelines, including ensuring that the study is conducted in accordance with the protocol. We will review all ongoing investigations of 18F-AV-1451 and give our evaluations of the safety and usefulness of this compound to the FDA and the IRB. We will keep all records per FDA and IRB guidelines and submit all amendments, IND safety reports and annual reports to the FDA and IRB.

Potential Benefits

This study will not benefit subjects directly. But the development of an early measure of tau deposition in this patient population would be a benefit as in diagnosis and a possible marker of treatment response.

References

- Buchhave P, Minthon L, Zetterberg H, Wallin AK, Blennow K, Hansson O (2012) Cerebrospinal fluid levels of betaamyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. Arch Gen Psychiatry 69:98-106.
- Chien DT, Bahri S, Szardenings AK, Walsh JC, Mu F, Su MY, Shankle WR, Elizarov A, Kolb HC (2013) Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. J Alzheimers Dis 34:457-468.
- Clark LN, Poorkaj P, Wszolek Z, Geschwind DH, Nasreddine ZS, Miller B, Li D, Payami H, Awert F, Markopoulou K, Andreadis A, D'Souza I, Lee VM, Reed L, Trojanowski JQ, Zhukareva V, Bird T, Schellenberg G, Wilhelmsen KC (1998) Pathogenic implications of mutations in the tau gene in pallido-ponto-nigral degeneration and related neurodegenerative disorders linked to chromosome 17. Proc Natl Acad Sci U S A 95:13103-13107.
- Lynch T, Sano M, Marder KS, Bell KL, Foster NL, Defendini RF, Sima AA, Keohane C, Nygaard TG, Fahn S, et al. (1994) Clinical characteristics of a family with chromosome 17-linked disinhibition-dementia-parkinsonismamyotrophy complex. Neurology 44:1878-1884. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ (2001) Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 58:1803-1809.
- Seeley WW, Crawford R, Rascovsky K, Kramer JH, Weiner M, Miller BL, Gorno-Tempini ML (2008) Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. Arch Neurol 65:249-255.
- Sperling RA, Karlawish J, Johnson KA (2013) Preclinical Alzheimer disease-the challenges ahead. Nat Rev Neurol 9:54-58.
- Zhang W, Arteaga J, Cashion DK, Chen G, Gangadharmath U, Gomez LF, Kasi D, Lam C, Liang Q, Liu C, Mocharla VP, Mu F, Sinha A, Szardenings AK, Wang E, Walsh JC, Xia C, Yu C, Zhao T, Kolb HC (2012) A highly selective and specific PET tracer for imaging of tau pathologies. J Alzheimers Dis 31:601-612.