Longitudinal evaluation of [^{18}F]MK-6240 as a novel tau PET radiotracer in patients with Alzheimer's disease dementia or mild cognitive impairment compared to healthy volunteers

NCT:03919669

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Brad Christian, PhD, University of Wisconsin-Madison holds the IND for [F-18]MK6240 (IND# 134, 516) and Sterling Johnson, PhD holds the IND for [C-11]PiB (IND# 107,114)

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1 PROTOCOL SYNOPSIS

TITLE	Longitudinal evaluation of [^{18}F]MK-6240 as a novel tau PET radiotracer in subjects with Alzheimer's disease or mild cognitive impairment compared to healthy volunteers
TEST PRODUCT	[^{18}F]MK-6240
STUDY CENTER	University of Wisconsin School of Medicine and Public Health
TRIAL OBJECTIVES	The overall goal of this protocol is to characterize the longitudinal change in tau burden using [^{18}F]MK-6240. Data from this study may be used to inform the design of future therapeutic trials utilizing [^{18}F]MK-6240 as a marker of disease progression. The primary objectives of this study are: • To characterize the longitudinal change in [^{18}F]MK-6240 brain uptake at 26 (6 months) and 52 (12 months) weeks compared to baseline in subjects with Alzheimer's disease (AD) dementia, mild cognitive impairment (MCI) and healthy volunteers (HV). This comparison may include 78 (18 month) week measures, if the 26 or 52 week measures are not available, in order to attain 6 month and 12 month intervals. • To correlate the changes in [^{18}F]MK-6240 uptake and changes in clinical cognitive assessments (MMSE, ADAS-cog and CDR) The secondary objectives of this study are: • To characterize the longitudinal change in [^{18}F]MK-6240 brain uptake at 104 (24 months) weeks compared to baseline in subjects with AD dementia, MCI and healthy volunteers. This comparison may include 130 (30 month) week measures, if two or more [^{18}F]MK-6240 scans are not available. • To evaluate cross-sectional comparison of [^{18}F]MK-6240 uptake in AD, MCI and HV at baseline 26, 52 and 104 weeks. This may include 78 (18 month) and/or 130 (30 month) week measures, if the 26, 52, or 104 week measures are not available.
STUDY DESIGN	This is a longitudinal, observational study evaluating the imaging characteristics of the tau PET radioligand [^{18}F]MK-6240 in AD, MCI and HV subjects. Up to 42 subjects including approximately 28 MCI/mild AD subjects, up to 5 moderate AD subjects, and 9 similarly aged HV subjects will be consented and screened. Imaging procedures include [^{11}C]PiB, [^{18}F]MK-6240 PET and structural MRI. All subjects who complete at least one [^{18}F]MK-6240 PET imaging session will be considered enrolled in the study. As many as 28 MCI/mild AD subjects, 5 moderate AD subjects, and 9 similarly aged HV subjects may complete an evaluable baseline [^{18}F]MK-6240 PET scan to enable at least 23 subjects (15 MCI/mild AD, 3 moderate AD, 5 HV subjects) to complete the 24 month follow up. Subjects who discontinue prior to completing the 12-month or 18-month [^{18}F]MK-6240 PET scan may be replaced in the study until a total of 15 patients (MCI/AD) complete the 12 month PET imaging session. Subjects that complete the 12-month visit but wish to abandon the study before the 24-month visit will be given the option to have a final evaluation any time between 18 and 24 months. All subjects will provide informed consent at enrollment before any study procedures are performed. The Screening procedures will occur within 60 days prior to baseline [^{18}F]MK-6240 imaging and will include a brief cognitive

	assessment, review of medical history and medications, physical examination, [^{11}C]PiB PET imaging and brain MRI. [^{11}C]PiB and MRI IMAGING: As part of the Screening Visit, subjects will complete structural brain MRI imaging which will be used for eligibility evaluation, co-registration with PET imaging and volumetric analysis. If an evaluable PiB scan has been acquired and is available for use in this study and occurred within 12 months of screening, the scan will not be repeated. Otherwise, [^{11}C]PiB PET imaging will be obtained at screening to evaluate for amyloid deposition. Subjects will be considered amyloid positive if [^{11}C]PiB DVR (distribution volume ratio) imaging demonstrates amyloid deposition based on qualitative read or DVR index value >1.20. For the [^{11}C]PIB PET imaging session, subjects will receive a single IV bolus injection target dose of 15 mCi $\pm$ 20% of [^{11}C]PIB and scanned dynamically for 70 minutes. For participants who may not be able to tolerate this long scan, a 20 minute scan will be offered after 50 minutes of uptake. [^{18}F]MK-6240 PET IMAGING VISITS: Subjects will complete [^{18}F]MK-6240 PET imaging at four time points: Baseline, 6 months, 12 months and 24 months. If unable to complete the 6 month, 12 month, or 24 month visit, an 18 month and/or 30 month visit may instead be scheduled, totaling a maximum of four time points. [^{18}F]MK-6240 is administered intravenously at a target dose of 185 MBq (5 mCi) plus or minus 20%. Image acquisition will occur from 70 to 110 minutes post-injection. Repeat of up to two [^{18}F]MK-6240 PET imaging scans may be completed if needed. Repeat scans will be prioritized for the Baseline and 12 month visits. A physician or physician representative will evaluate the subject for adverse events prior to leaving the imaging center and will discharge subjects when determined medically stable. A follow-up phone call to the subject will be conducted by study staff within 4 days (±2 days) post-injection of [^{18}F]MK-6240 to confirm subject well-being and to collect information regarding new adverse or ongoing events. The primary outcome for [^{18}F]MK-6240 imaging will be the standardized uptake value ratio (SUVR). The reference region is the inferior cerebellum gray matter. A standardized volume of interest (VOI) template will be used to quantitatively measure [^{18}F]MK-6240 tracer uptake in regions with expected tau pathology.
INCLUSION/ EXCLUSION CRITERIA	Healthy volunteer subjects and MCI/AD patients who are medically stable and meet the inclusion criteria and do not meet any of the exclusion criteria will be eligible for enrollment into the study. **Inclusion Criteria for All Subjects** • Signed and dated written informed consent must be obtained from the subject to enter the study and before any assessment is performed. • Pregnancy: Participant is not pregnant at the time of the PET and MRI imaging exams. Urine pregnancy tests will be conducted as needed with pre-menopausal women who are of child-bearing potential.

- Willing and able to undergo study procedures and study schedule
- Availability of a study partner who has frequent and sufficient contact with the subject and is able to provide accurate information regarding the subject's cognitive and functional abilities for the CDR, agrees to accompany the subject and provide information at visits or is available by phone. The study partner must have sufficient cognitive capacity, in the judgment of the investigator, to accurately report upon the subject's behavior and cognitive and functional abilities.
- Males and females between the age of 50 and 85 (inclusive).
- Healthy with no clinically relevant finding on physical examination at screening and upon reporting for the Baseline [^{18}F]MK-6240 imaging visit.

Inclusion Criteria for Healthy Volunteer Subjects (HV)

- Normal Cognition based on cognitive results at screening.
- Healthy with no clinically relevant finding on physical examination at screening and upon reporting for the Baseline [^{18}F]MK-6240 imaging visit.
- CDR global score =0

Inclusion Criteria for Subjects with a Diagnosis of MCI or Dementia Due to AD

- Have screening [^{11}C]PiB PET imaging demonstrating amyloid binding based on qualitative read or DVR index value >1.20.
- MMSE score 26-30 (inclusive), CDR global score 0.5 for subjects with MCI
- MMSE score 22-26 (inclusive), CDR global score 0.5 or 1 for subjects with mild dementia due to AD
- MMSE score 16-21 (inclusive), CDR global score 1-2 for subjects with moderate dementia due to AD
- Subjects with MCI must meet 2018 research criteria for MCI (Jack et al., 2018).
- Subjects with dementia must meet 2018 research criteria for dementia (Jack et al., 2018).
- A structural brain MRI with no evidence of non-AD disease to account for dementia or MRI exclusion criteria.

Exclusion Criteria (for all subjects)

- Lack of capacity to provide informed consent at study entry.
- Subject has received an investigational drug or device within 30 days of screening. Other experimental PET radiotracer drugs are not excluded.
- For women, pregnant, lactating or breastfeeding or intention to become pregnant.
- Evidence of unstable or untreated clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematological, neoplastic, endocrine, alternative neurological, immunodeficiency, pulmonary, or other disorder or disease. Stable, treated chronic medical conditions like hypertension, hypercholesterolemia, diabetes mellitus, non-metastatic dermatologic or prostatic cancer, etc. are acceptable as long as they do not, in the study investigator's opinion, contribute to cognitive dysfunction or limit participation in study procedures.
- Any illness or other consideration that makes it unlikely that the subject will be able to complete the 26-month study.

	• Current or prior history (within past 5 years) of significant alcohol or substance abuse as determined by the investigator. • Psychiatric disorders that may interfere with the study including current major Axis I DSM-V disorders including but not limited to severe Major depression, current or history of bipolar I disorder, or schizophrenia. • Non-English speakers or subjects who are unable to comprehend study materials are excluded at entry • MRI exclusion criteria include: Findings that may be responsible for neurologic status of the subject such as significant evidence of cerebrovascular disease with multiple infarcts, infectious disease, space-occupying lesion, normal pressure hydrocephalus, CNS trauma, or any other structural abnormality that may impact cognition or image analysis, as judged by the investigator. • MRI-incompatible implants or devices such as certain cardiac pacemakers or defibrillators, insulin pumps, cochlear implants, metallic ocular foreign body, implanted neural stimulators, CNS aneurysm clips and other medical implants that have not been certified for MRI, or history of claustrophobia in MRI that prevents completion of MRI protocol. • Treatment with any therapeutic molecule that targets Aβ or tau within 12 months prior to screening.
LENGTH OF STUDY	For each subject participating, the duration of study participation will be approximately 26 months including a 60-day screening period and 24-month longitudinal assessment period. The longitudinal assessment period may be extended to include a 30-month visit, if prior visits are missing. If a 30-month visit is scheduled, the total duration will be approximately 32 months.
INVESTIGATIONAL AGENTS	[^{18}F]MK-6240 and [^{11}C]PiB are investigational PET radiotracers that will be synthesized in accordance with FDA IND applications for each tracer. All subjects will receive one injection of [11C]PiB (at screening only) and up to four injections of [^{18}F]MK-6240 during the course of their participation in this 26-32 month study. Repeat of up to two [^{18}F]MK-6240 PET imaging scans may be completed if needed. Repeat scans will be prioritized for the Baseline and 12 month visits.
STATISTICAL METHODS	
DEMOGRAPHICS	The demographic and baseline characteristics will be summarized according to the clinical group (HV, MCI and AD) using descriptive statistics for continuous variables and using frequency count and percentage for discrete variables.
ANALYSIS OF STUDY OBJECTIVES	The change in [^{18}F]MK-6240 uptake (e.g. composite and regional SUVR, voxel based statistics or change in tau distribution) will be determined by estimating the change from Baseline to each follow-up visit (6, 12 and 24 months). If the 6, 12, or 24 month visit measures are not available, this may include 18 and/or 30 month visit measures. The change in [^{18}F]MK-6240 uptake will be compared among the groups (AD, MCI and HV subjects) aligned on intervals of 6, 12, 18 and 24 months. The relationship between the change in [^{18}F]MK-6240 uptake (e.g. composite and regional SUVR, voxel based statistics or change in tau distribution) and change in clinical severity or cognitive outcomes will be analyzed in AD dementia, MCI and

HV subjects. In addition, the correlation between baseline [^{18}F]MK-6240 uptake and baseline clinical endpoints will be evaluated in all subjects.

Cross-sectional comparisons will be made among the clinical groups (AD, MCI and HV subjects) at Baseline, 6, 12 and 24 months for the following measures: [^{18}F]MK-6240 uptake (composite and regional SUVR), neuropsychological testing (MMSE, CDR, ADAS-cog), MRI markers of atrophy such as hippocampal volume. If the 6, 12, or 24 month visit measures are not available, this cross-sectional comparison may include 18 and/or 30 month measures.

2 BACKGROUND AND RATIONALE

2.1 Background

Neurofibrillary tangles begin during the preclinical phase of AD, and by the time of very mild dementia neurofibrillary tangles are well formed in predictable staged patterns (Braak & Braak, 1990; Braak, Braak, & Bohl, 1993). However, the rate of temporal change in neurofibrillary tangle burden in individual cases is poorly understood.

Up until recently, the information about the temporal and spatial signal from neurofibrillary tangle (tau related) pathology in AD has come from neuropathology studies of brain bank cases (Gomez-Isla et al., 1996) and in life from CSF tau protein levels which have no spatial information and suffer from lack of standardized assays from lab to lab (Mattsson et al., 2013). The advent of tau positron emission tomography (PET) imaging using compounds (Chien et al., 2014; Maruyama et al., 2013; Villemagne et al., 2014) such as [F-18]AV1451 and now [F-18]MK6240 (Hostetler et al., 2016; Lohith et al., 2018) hold promise of making major breakthroughs in diagnosing AD accurately and characterizing its rate of progression. Our group has published one of the first clinical papers (Betthauser et al., 2018) on MK-6240 describing its temporal properties and imaging characteristics. World-wide the field has now conducted over 4000 exams with this compound and find it safe with no radioligand-related serious adverse events and strong binding to AD-relevant brain regions in amyloid positive subjects in a pattern consistent with the neuropathology literature (see **Figure 1**).

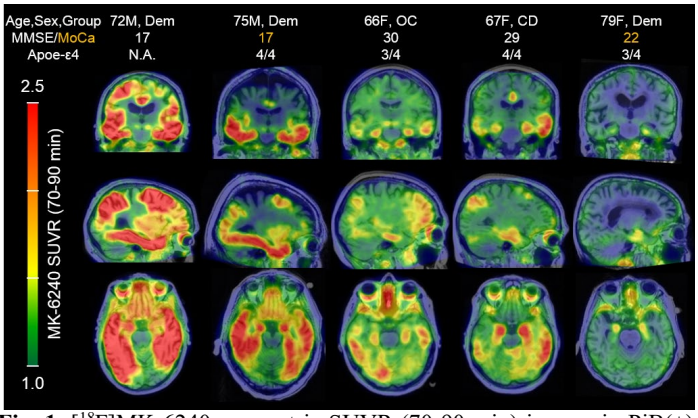

Fig. 1. [^{18}F]MK-6240 parametric SUVR (70-90 min) images in PiB(+) individuals organized by image-based Braak stages. [^{18}F]MK-6240 spatial binding patterns in PiB(+) individuals recapitulated patterns consistent with neuropathological staging of Alzheimer's disease, including in the hippocampus. The PiB(+) dementia case in the far rightward column was clinical diagnosed with probable AD dementia (not informed by these biomarkers) but exhibited only circumscribed [^{18}F]MK-6240 signal in the entorhinal region.

Molecular imaging biomarkers have the potential to play a key diagnostic role in tauopathies. Tau protein has been identified as one of the key pathological features of AD. Tau is the primary protein composing neurofibrillary tangles and unlike beta-amyloid deposition, post-mortem studies have shown that neurofibrillary tangle density correlates with neurodegeneration and cognitive impairment. Thus, a PET imaging agent that binds to aggregated tau has the potential to serve as a biomarker for disease severity or neurodegeneration and may be useful for monitoring disease progression in therapeutic trials. PET is able to detect the spatial distribution of the radioactive compound in the brain and can be used as an objective, sensitive, and accurate method to quantify the concentration of the target site in different brain regions. Using these PET techniques, β-amyloid aggregates have been successfully imaged in several studies in AD patients using high affinity 11-C and 18-F-labeled PET tracers such as PiB or florbetapir (see Johnson, 2018 for a review; Villemagne et al., 2013; Villemagne et al., 2012).

2.2 Rationale for choice of amyloid imaging radiotracer:

[^{11}C]PIB is the first of the amyloid imaging agents and is still considered the best of these agents for its overall imaging properties including lower non-specific off-target white matter binding and its large dynamic range (Villemagne et al., 2012). [^{11}C]PIB utilizes carbon 11 which is fast-decaying (20 minute half-life). While a distinct advantage for such a fast-decaying tracer is a much lower radiation exposure to the body, its short half life makes it unwieldy for wide commercial distribution. Thus, even though [^{11}C]PIB offers the best image characteristics and lowest radiation exposure (about 3mSv which is less than 1/3rd of the dosage of newer F18 agents, about 10mSV), it was never feasible to produce commercially in large scale and FDA approval was not ever sought by its developers. Each dose must be manufactured locally under IND. Since its initial discovery in 2004, four other agents have been discovered ([18F]NAV, [18F]florbetapir, [18F]florbetaben, [18F]flutemetamol) and three of these have gone through the requisite process to obtain FDA approval—[^{18}F]florbetapir, [^{18}F]florbetaben, and [^{18}F]flutemetamol. All of the FDA approved tracers have inferior imaging properties when compared to PIB, but to their advantage they are also Fluorine-18 based with a much longer half-life (~110 minutes) which allows them to be manufactured at central specialized manufacturing sites and distributed regionally throughout the country. (This is similar conceptually to how hospitals such as the UWHC purchase [^{18}]FDG for clinical use from an external vendor.)

While the F18 radiotracers have improved the accessibility to amyloid imaging for research and gradual clinical use, PIB remains the gold standard to which other amyloid radiotracers are compared (Klunk et al., 2015). This is due to 1) its wider dynamic range which may improve its sensitivity to earlier stages of amyloid elevation 2) its relatively better target-specific binding pattern such that it binds largely only to the fibrillar amyloid plaques, while F18 agents are more lipophilic and characteristically bind to off-target myelin-containing brain regions including very high binding in the white matter and thalamus making it difficult to accurately visually rate and quantify signal that is due to true amyloid signal versus off-target 'spill in' effects into tissue of interest.

In a series of studies, PiB has demonstrated high agreement with histopathology for identifying amyloid plaques (Bacskai et al., 2007; Ikonomovic et al., 2008; Joie et al., 2018; Leinonen et al., 2008). PiB differentiates AD cases from controls in vivo (Klunk et al., 2004), and predicts subsequent cognitive decline in cognitively normal adults (Clark et al., 2018; Clark et al., 2016; Donohue et al., 2017), and conversion to dementia in patients with MCI (Chen et al., 2014; Frings et al., 2018; Hatashita & Wakebe, 2017; Iaccarino et al., 2017; Kemppainen et al., 2014; Kikukawa et al., 2018; Trzepacz et al., 2014; Wolk et al., 2009).

Comparison to Florbetaben

Villemagne et al. (Villemagne et al., 2012) compared 20 people (10 AD dementia and 10 controls) with [^{11}C]PIB and [^{18}F]Florbetaben. The correlation of global amyloid burden as estimated with each tracer was r=.97. However the effect-size was nearly uniformly higher (by 10%) for PIB than florbetaben.

Comparison to Florbetapir

Wolk and colleagues (Wolk et al., 2012) compared [11C]PiB to [18F]Florbetapir in 12 AD cases and 14 healthy control subjects of similar age. Global beta-amyloid composite scores were computed in parallel fashion and correlated. The Pearson coefficient was r= .78. The area under the curve for separating cases from controls was 1.0 for PIB and .90 for florbetapir. The authors concluded that florbetapir provides comparable information to PiB.

Comparison to Flutemetamol

At least five studies have compared agreement between PIB and [18F]Flutemetamol and all report very strong robust agreement (Adamczuk et al., 2016; Leinonen et al., 2013; Lowe et al., 2017; Mountz et al., 2015; Vandenberghe et al., 2010). Mountz et al. (2015) report a correlation greater than 0.90 in global amyloid burden and strong agreement (.82 kappa coefficient) for visual rating. Adamzuck found the concordance between PIB and flutemetamol of =94% for amyloid positivity and r=.84 for the global index score semiquantitative composite. Leinonen et al (2013) and Vandenberghe et al. (2010) reported correlations of .97 and .90 respectively.

Summary: PIB is the standard for comparison for the F18 amyloid agents. PiB corresponds strongly to amyloid pathology at autopsy, separates cases from controls with AUCs at or near 1.0 (Lowe et al., 2017) and PIB elevation in controls and MCI is correlated with high specificity to later decline and conversion to dementia. The F18 agents are strongly correlated to PiB. The higher radiation dose of the F18 agents, and their higher off-target binding to white matter (lipophilicity) make them less optimal than PiB for detecting and quantifying amyloid plaques *in vivo* in a clinical research setting.

2.3 Rationale for imaging tau with [F-18]MK6240

The ability to image brain amyloid has offered an important advance for the diagnosis of neurodegenerative conditions (Jack et al., 2018; Johnson, 2018). In contrast to Aβ-rich neuritic and diffuse amyloid plaques, the density and distribution of pathological tau, aggregated in neurofibrillary tangles, increases with AD-related cognitive impairment and correlates with neurodegeneration. But the spatiotemporal rate of progression in the brain within individual people is not well understood. This information is needed in order to appropriately plan intervention trials. Furthermore, first generation tau tracers such as AV1451 and THK5351 have been shown to have off-target binding effects in regions relevant to AD, which poses challenges to treatment trials wishing to demonstrate target engagement with those compounds.

[^{18}F]MK-6240 has been developed as a highly specific positron emitting radiopharmaceutical for *in vivo* imaging of tau protein aggregates (Hostetler et al., 2016; Lohith et al., 2018). [^{18}F]MK-6240 has been previously evaluated by several groups including ours demonstrating substantial NFT deposition in the AD subjects and no or little evidence for tau binding in the HV subjects in the absence of amyloid. This study aims to evaluate the longitudinal change in tau burden using [^{18}F]MK-6240 PET imaging in relation to cognitive and functional metrics.

2.4 Human Safety and Tolerability

[^{18}F]MK-6240 has been evaluated in over 1000 subjects world-wide in several studies including over 240 at the UWSMPH and is well tolerated with no known radioligand-related serious adverse events.

3 STUDY PURPOSE

The overall goal of this study is to evaluate the longitudinal change in the uptake of [^{18}F]MK-6240. The data obtained will be vital in forming hypotheses for future larger studies, particularly for hypotheses about effect sizes that may inform future large scale clinical trials.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objectives of this study are:

- To characterize the longitudinal change in [^{18}F]MK-6240 brain uptake at 26 and 52 weeks compared to baseline in subjects with dementia due to AD, mild cognitive impairment (MCI) and healthy volunteers (HV). This comparison may include 78 (18 month) week measures, if the 26 or 52 week measures are not available, in order to attain 6 month and 12 month intervals.
- To correlate the changes in [^{18}F]MK-6240 uptake and changes in clinical cognitive assessments (MMSE, ADAS-cog and CDR).

4.2 Secondary Objectives

The secondary objectives of this study are:

- To characterize the longitudinal change in [^{18}F]MK-6240 brain uptake at 104 (24 months) weeks compared to baseline in subjects with dementia due to AD, mild cognitive impairment and healthy volunteers. This comparison may include 130 (30 month) week measures, if two or more prior [^{18}F]MK-6240 scans are not available.
- To evaluate cross-sectional comparison of [^{18}F]MK-6240 uptake in AD, MCI and HV at baseline 26, 52 and 104 weeks. This cross-sectional comparison may include 78 (18 month) and/or 130 (30 month) week measures, if the 26, 52, or 104 week measures are not available.

Table 1. Overview of study design and timeline

Screening	Baseline	6 month[1]	12 month[1]	18 Month[3]	24 month[2]	30 Month[3]
Within -60 to -1 days of baseline	0 weeks (day 0)	26 weeks (±60 days)	52 weeks (±60 days)	78 weeks (±60 days)	104 weeks (±60 days)	130 weeks (±60 days)
Cognitive Testing (MMSE, CDR, ADAS-cog)	No Cognitive Testing	Cognitive Testing (MMSE, CDR)	Cognitive Testing (MMSE, CDR, ADAS-cog)	Cognitive Testing (MMSE, CDR, ADAS-cog[4])	Cognitive Testing (MMSE, CDR, ADAS-cog)	Cognitive Testing (MMSE, CDR, ADAS-cog[5])
MRI (T1, T2)	No MRI	MRI	MRI	MRI	MRI	MRI
Amyloid Imaging (^{11}C-PiB)	No Amyloid Imaging	No Amyloid Imaging	No Amyloid Imaging	No Amyloid Imaging	No Amyloid Imaging	No Amyloid Imaging
No [^{18}F]MK-6240 PET Imaging	[^{18}F]MK-6240 PET Imaging	[^{18}F]MK-6240 PET Imaging	[^{18}F]MK-6240 PET Imaging	[^{18}F]MK-6240 PET Imaging	[^{18}F]MK-6240 PET Imaging	[^{18}F]MK-6240 PET Imaging

Footnotes:
1: If the 6 and/or 12 month visit is not completed, an 18 and/or 30 month visit may be completed, totaling a maximum of 4 timepoints.
2: If the 24 month visit is not completed, a 30 month visit may be completed
3: The 18 month and/or 30 month visit may be scheduled if 6 month, 12 month, and/or 24 month visit is missing
4: ADAS-cog will be completed at 18 month visit if 12 month visit is not completed
5: ADAS-cog will be conducted at the final visit including the 30-month visit

5 STUDY DESIGN

This is a longitudinal, observational study evaluating the imaging characteristics of the tau PET radioligand [^{18}F]MK-6240 in AD, MCI and HV subjects. Up to 28 MCI/mild AD subjects, up to 5

moderate AD subjects, and up to 9 similarly aged HV subjects will be enrolled at the University of Wisconsin-Madison. Recruitment as well as screening and longitudinal clinical activities, including MRI, [^{11}C]PiB and [^{18}F]MK-6240 PET imaging, will be completed. The general design of the study is provided in **Table 1**.

The overall goal of this protocol is to evaluate the longitudinal change in uptake of [^{18}F]MK-6240, an NFT targeted radiopharmaceutical. Data from this study may be used to inform the design of future therapeutic trials utilizing [^{18}F]MK-6240 as a marker of disease progression.

Participants will be recruited from the Wisconsin Alzheimer's Disease Research Center (ADRC), the Wisconsin Registry for Alzheimer's Prevention (WRAP) as well as from the community. Pertinent standard lab tests and findings from the referral source (such as diagnosis, medical history and prior cognitive results) will be reviewed to assess eligibility.

5.1 Study Location:

The study will take place at the University of Wisconsin-Madison medical campus including the following sites:

Waisman Center Laboratory for Brain Imaging and Behavior: where the MRI and PET/CT brain imaging will take place and radiolabeling, and chemistry occur.

University Hospital and Clinics or WIMR where wide-bore MRI scanners are located that will be utilized if participant size prohibits the standard 3T scanners.

Alzheimer's Disease Research Center (ADRC) Imaging Core in the Clinical Sciences Center (University Hospital) which is adjacent to WIMR and across the street from Waisman Center. At the ADRC Imaging Core Directed by Dr. Johnson, the images will be backed up and maintained and processed using standardized pipelines.

5.2 Enrollment Window and Study Duration:

Recruitment and enrollment will require approximately 6 months. The study duration is 26 months inclusive of 2 months for screening and baseline activities and 24 months of follow-up activities. The longitudinal assessment period may be extended to include a 30-month visit, if needed. If a 30-month visit is scheduled, the total duration will be approximately 32 months.

6 SELECTION AND ENROLLMENT OF PARTICIPANTS

Healthy volunteers and subjects diagnosed with mild cognitive impairment (MCI) and dementia cases will be enrolled who meet the following criteria.

6.1 Inclusion Criteria (for all subjects)

- Signed and dated written informed consent must be obtained from the subject to enter

the study and before any assessment is performed.

- Pregnancy: Participant is not pregnant at the time of the PET and MRI imaging exams. Urine pregnancy tests will be conducted as needed with pre-menopausal women who are of child-bearing potential.
- Willing and able to undergo the study procedures and study schedule.
- Availability of a study partner whohas frequent and sufficient contact with the subject and is able to provide accurate information regarding the subject's cognitive and functional abilities for the CDR, agrees to accompany the subject and provide information at visits or is available by phone. The study partner must have sufficient cognitive capacity, in the judgment of the investigator, to accurately report upon the subject's behavior and cognitive and functional abilities.
- Males and females between the age of 50 and 85 (inclusive).
- Healthy with no clinically relevant finding on physical examination at screening and upon reporting for the Baseline [^{18}F]MK-6240 imaging visit.

6.2 Inclusion Criteria for Healthy Volunteers

- Normal cognition based on cognitive results at screening
- Healthy with no clinically relevant findings on physical examination at screening and upon reporting for the baseline visit
- CDR global score = 0

6.3 Inclusion Criteria for Subjects with a Diagnosis of MCI or Dementia due to AD

- Have screening [11C]PiB PET imaging demonstrating amyloid binding based on qualitative read or DVR index value >1.20.
- MMSE score 26-30 (inclusive), CDR global score 0.5 for subjects with MCI
- MMSE score 22-26 (inclusive), CDR global score 0.5 or 1 for subjects with mild dementia due to AD
- MMSE score 16-21 (inclusive), CDR global score 1-2 for subjects with moderate dementia due to AD
- Subjects with MCI must meet 2018 research criteria for MCI (Jack et al., 2018).
- Subjects with dementia must meet 2018 research criteria for dementia (Jack et al., 2018).
- A structural brain MRI with no evidence of non-AD disease to account for dementia or MRI exclusion criteria.

6.4 Exclusion Criteria

Candidates meeting any exclusion criteria at screening are not eligible for inclusion:

- Lack of decisional capacity to provide informed consent at study entry.
- Subject has received an investigational drug or device within 30 days of screening. Other experimental PET radiotracer drugs are not excluded.
- For women, pregnant, lactating or breastfeeding or intention to become pregnant.

- Evidence of unstable or untreated clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematological, neoplastic, endocrine, alternative neurological, immunodeficiency, pulmonary, or other disorder or disease. Stable, treated chronic medical conditions like hypertension, hypercholesterolemia, diabetes mellitus, non-metastatic dermatologic or prostatic cancer, etc. are acceptable as long as they do not, in the study investigator's opinion, contribute to cognitive dysfunction or limit participation in study procedures.
- Any illness or other consideration that makes it unlikely that the subject will be able to complete the 26-month study.
- Current or prior history (within past 5 years) of significant alcohol or substance abuse as determined by the investigator.
- Psychiatric disorders that may interfere with the study including current major Axis I DSM-V disorders including but not limited to severe Major depression, current or history of bipolar I disorder, or schizophrenia.
- Non-English speakers or subjects who are unable to comprehend study materials are excluded at entry
- MRI exclusion criteria include: Findings that may be responsible for neurologic status of the subject such as significant evidence of cerebrovascular disease with multiple infarcts, infectious disease, space-occupying lesion, normal pressure hydrocephalus, CNS trauma, or any other structural abnormality that may impact cognition or image analysis, as judged by the investigator.
- MRI-incompatible implants or devices such as certain cardiac pacemakers or defibrillators, insulin pumps, cochlear implants, metallic ocular foreign body, implanted neural stimulators, CNS aneurysm clips and other medical implants that have not been certified for MRI, or history of claustrophobia in MRI that prevents completion of MRI protocol.
- Treatment with any therapeutic molecule that targets Aβ or tau within 12 months prior to screening.

6.5 Study Enrollment Procedures

- Physicians who hold UW memory clinics may refer their clinically diagnosed cases of MCI or dementia by asking their patient to fill out a permission to contact form which includes the patient's name and contact details and declares an interest in learning more about the study. A study information sheet is also provided. Following return of permission to contact form, the patient will be contacted by the study team, and the study will be explained per the phone screening script. The phone screening script also contains an oral consent and HIPPA authorization for medical records review. The study team will conduct the eligibility checklist with the patient and will access medical records with oral consent. Medical records may be requested with oral

consent to evaluate eligibility including current diagnoses and medications, cognitive status, and prior head imaging.

- For ADRC clinical core(2015-0030) and WRAP (2016-0634) participants, the applicable source study staff will conduct database screens for participants who meet criteria for older controls or patient groups. Dr. Johnson, the PI of this protocol, is also PI of WRAP and an investigator for the ADRC clinical core protocol.
- From this general pool, case records will be examined further for eligibility criteria. Candidates who are ostensibly eligible on the record review will be contacted by a source study staff member via letter or phone and invited to participate. Reasons for non-participation of eligible unscreened candidates will be logged.
- Interested candidates will be phone screened. If all eligibility criteria are met, the participant will have the in person screening visit to involve cognition, physical exam and MRI and PiB. A screening log will be kept to record reasons for screen failures. A waiver of written consent is requested for the phone screen. Interested candidates will undergo verbal consent before screening information is collected via phone.
- Informed consent is required prior to procedures. Only individuals with capacity to consent at screening will be included. For participants diagnosed with Alzheimer's disease, this will be assessed by study clinicians or psychologists using a brief interview format based on questions on the Consent form. For all others, this is with the study coordinator. After enrollment, subjects who decline to the point where they no longer have capacity to consent will be allowed to continue because they initially expressed this desire on the enrollment consent form.
- In the event that reconsent is needed during the course of the study, capacity will be reassessed at that time. If a participant is found to lack decisional capacity to consent based on the brief interview, they will be allowed to continue because they initially expressed this desire on the enrollment consent form. In this case, assent (the participant's desire to continue to participate or not participate in the research) will always be obtained, as well as surrogate consent. The surrogate would be sought in the following order of priority: participant's research power of attorney/research advance directive, guardian or healthcare power of attorney, or next of kin. Next of kin includes (in the following order): spouse, adult child, parent, adult sibling, grandparent, adult grandchild, or a close friend of the participant. Participant's assent will always operate as a veto to the participant's participation, despite the surrogate's preference.

Table 2. Schedule of Events

	Screening Assessments	Baseline (BL)	6 Month Assessments[5]	12 Month Assessments[5]	18 Month Assessments[4]	24 Month Assessments[6]	30 Month Assessments[4]	Early Termination Assessments
		Within 60 d of Screening	26 w from BL (±60 days)	52 w from BL (±60 days)	78 w from BL (±60 days)	104 w from BL (± 60 days)	130 w from BL (±60 days)	
Inclusion/Exclusion Criteria	X	X	X	X	X	X	X	X
Demography and Smoking History	X	X	X	X	X	X	X	X

Informed Consent	X	X[AN]	X[AN]	X[AN]	X[AN]	X[AN]	X[AN]	X[AN]
Medical History	X							
Physical & Neurologic Examination[1]	X	X[AN]	X[AN]	X[AN]	X[AN]	X[AN]	X[AN]	X[AN]
Medications review	X	X	X	X	X	X	X	X
Height/weight	X	X	X	X	X	X	X	X
MMSE & CDR	X		X	X	X	X	X	X
ADAS-cog	X			X	X[3]	X	X	X
Vital Signs (blood pressure, pulse rate, respiratory rate)	X	X	X	X	X	X	X	X
Review NIA-AA AD/MCI criteria	X							
Pregnancy Test (if applicable)[2]	X	X	X	X	X	X	X	X
Brain MRI (T1, T2)	X		X	X	X	X	X	X
[^{11}C]PiB	X							
[18F]MK-6240		X	X	X	X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X	X
F/U phone call within 4 days	X	X	X	X	X	X	X	X

Footnotes:
AN: As needed
1: Physical exam at screening may be performed at investigator's discretion to ensure eligibility
2:Pregnancy test administered to WOCBP, as defined by ADRC pregnancy testing SOP
3: ADAS-cog will be completed at 18 month visit if 12 month visit is not completed
4: The 18 month and/or 30 month visit may be scheduled if 6 month, 12 month, and/or 24 month visit is missing
5: If the 6 and/or 12 month visit is not completed, an 18 and/or 30 month visit may be completed, totaling a maximum of 4 timepoints.
6: If the 24 month visit is not completed, a 30 month visit may be completed

7 STUDY PROCEDURES

7.1 Description of Evaluations and Procedures

Procedures including screening/eligibility procedures and study visits are according to the schedule of events in **Table 2**.

7.1.1 Consenting Procedure

Before any study procedures are performed, informed consent will be obtained. A single consent form and process will be used for the screening and main study visits. The study coordinator or one of the study investigators will obtain written informed consent and the original document retained by the study team. At each subsequent visit the procedures for the visit are explained together with their major risks and the subject is asked if they wish to continue. It is always reiterated that the subject may change their mind at any point for any reason and stop participating. In the event that reconsent is needed during the course of the study, capacity will be reassessed at that time. If a participant is found to lack decisional

capacity to consent based on the brief interview, they will be allowed to continue because they initially expressed this desire on the enrollment consent form. In this case, assent (the participant's desire to continue to participate or not participate in the research) will always be obtained, as well as surrogate consent. The surrogate would be sought in the following order of priority: participant's research power of attorney/research advance directive, guardian or healthcare power of attorney, or next of kin. Next of kin includes (in the following order): spouse, adult child, parent, adult sibling, grandparent, adult grandchild, or a close friend of the participant. Participant's assent will always operate as a veto to the participant's participation, despite the surrogate's preference.

7.1.2 Screening Evaluation

Screening procedures will occur within 60 days prior to the Baseline assessment with [^{18}F]MK-6240 PET imaging, and will include collection demographic and other health related information (age, gender, ethnicity, race,), cognitive testing (MMSE, CDR and ADAS-cog), review of medical history and medications, tobacco use including smoking status (active or not), pack-year, duration of smoking, consumption during the last 6 months (#pack per day), physical and neurological examination. All subjects will complete these clinical assessments to ensure the subject is medically stable to complete the study protocol. In addition, [^{11}C]PiB PET/CT imaging will be completed for all subjects and serves as part of the screening process to confirm presence of amyloid deposition. Brain MRI (structural T1, T2) will be obtained at screening for eligibility evaluation and analysis of neurodegeneration.

7.1.3 Physical and Neurological Examination

A brief physical and neurological examination will include the examination of general appearance, neck (including thyroid), lungs, heart, lymph nodes, vascular and neurological. The physical exam at screening may be performed at the investigator's discretion to ensure the participant's eligibility. A recent physical exam from the referring physician may be used to ensure eligibility throughout the course of the study.

Information for all physical and neurological examinations will be included in the source documentation. Significant findings that are present prior to injection of [^{18}F]MK-6240 will be included in the medical history in the subject's source documents. Significant findings noted after injection of [^{18}F]MK-6240, which meet the definition of an adverse event will be recorded as an adverse event.

Urine pregnancy tests will be conducted as needed with pre-menopausal women who are of child-bearing potential.

7.1.4 Vital signs

Vital signs include BP, respiratory rate, and pulse measurements. Vital signs will be obtained before and after each PET imaging procedure.

7.1.5 Height and weight

Height and body weight (in indoor clothing) will be measured at the screening and main study visits.

7.1.6 Clinical Scales

7.1.6.1 Mini-Mental Status Exam (MMSE)

The MMSE is a sensitive, valid and reliable 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is commonly used as screening tool for dementia. It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time; thus, making it an effective way to document an individual's response to treatment.

Administration of the test takes between 5–10 minutes and examines functions including registration, attention and calculation, recall, language, ability to follow simple commands and orientation. This test is not a mental status examination. The standard MMSE form, which is currently published by Psychological Assessment Resources, is based on its original 1975 conceptualization, with minor subsequent modifications by the authors.

7.1.6.2 Clinical Dementia Rating Scale (CDR)

The CDR was developed at the Memory and Aging Project at Washington University School of Medicine in 1979 for the evaluation of staging severity of dementia. It was developed primarily for use in persons with dementia of the Alzheimer type (the equivalent of probable Alzheimer's Disease) and it can also be used to stage dementia in other illnesses as well.

The information from which the CDR score is derived consists of a standard set of information collected in a clinical instrument that uses other well-known scales for some of its foundation. The CDR Global Score will be used in this study as an eligibility criterion. In assigning a Global CDR, the six domains that are used to construct the overall CDR table are each scored individually. The six domains are: Memory, Orientation, Judgment and Problem-solving, Community Affairs, Home and Hobbies, and Personal Care. In rating each of these domains, the assessment should be based on the subject's cognitive ability to function in these areas. If they are limited in performing activities at home because of physical frailty, this should not affect their scoring on the CDR, which again should be rated on their cognitive ability alone. Each domain is rated on a 5-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment (personal care is scored on a 4-point scale without a 0.5 rating available).

7.1.6.3 Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog)

The ADAS-Cog is one of the most frequently used tests to measure cognition in clinical trials in AD. The ADAS-Cog is a more thorough battery than the Mini Mental State Exam, and primarily measures language and verbal episodic memory. The ADAS-Cog consists of 13 items and takes approximately 25 minutes to administer. The ADAS was developed as a two-part scale: one that measured cognitive functions and one that measured non-cognitive functions

such as mood and behavior. Most current research, including this study, uses the ADAS-Cog, which is the sub-scale that measures cognitive ability.

7.1.7 The MRI Protocol:

If the participant otherwise meets all inclusion and no exclusion criteria, the MRI will be performed. This procedure includes a T1-weighted anatomic volume, and a T2weighted fluid attenuated inversion recovery (FLAIR) scan to determine whether the brain is normal. These sequences do not take the place of a clinical MRI examination. If clinically significant abnormalities are found, the participant is excluded and referred for further clinical follow-up.

The MRI exams will be performed using a 3T MRI scanner at the Waisman Center or WIMR using the standardized ADRC MRI. Alternatively, a UW Hospital wide bore scanner may be utilized for MRI for larger participants. The scan duration is typically 45 minutes and no longer than 75 minutes and consists of established as well as innovative locally developed scan sequences.

The MRI procedure is considered complete if a T1-weighted volume and FLAIR scan are successfully acquired. When feasible, additional scans will be acquired. The additional sequences will make it possible to conduct exploratory comparisons. Sequences may include:

T1w Brain Volume: This sequence that provides high-resolution isotropic 1 mm voxels for volume and region quantification. This sequence is required and used for quantifying the PET images.

T2 Fluid attenuated inversion recovery (FLAIR): This is a 3D volume acquisition and is sensitive to ischemic disease and other pathology. This scan will be used to quantify white matter hyper-intensity lesion burden.

Other non-required MRI sequences. Additional sequences from the ADRC/WRAP standard protocol may be used to maintain continuity with prior and future MRIs with the program. These are performed when time schedule and tolerability permit and will be used to conduct exploratory analyses.

T2-weighted volume and susceptibility weighted scans: These are product sequences and are used for tissue segementation and for radiology reads respectively.

Quantitative T1 Mapping with MPNRAGE [experimental]: This is a locally developed anatomical sequence for detailed T1-mapping and tissue segmentation. This is a non-standard sequence conducted in Research mode.

Diffusion Imaging [experimental] A diffusion-weighted may be performed used for whole brain advanced DTI studies. Diffusion encoding will be performed using multiple shells and multiple directions requisite for NODDI and advanced DTI modeling of white matter tracts.

Pseudo-continuous arterial spin labeling (pCASL) [experimental] provides a perfusion weighted scan used to assess flow and aspects of neurovascular function.

4D flow [experimental]: We will use a novel high-resolution flow-sensitive MRI approach to quantify macroscopic CBF in all extracranial and intracranial arteries in a single acquisition. The method developed at UW uses radial undersampling and significantly reduces otherwise prohibitively long scan times for a vascular examination uses *no* exogenous contrast agent. The method allows for coverage of the entire brain, providing high spatial resolution (0.6 mm isotropic) and flow dynamics within a 7-minute exam. This is a non-standard sequence conducted in Research mode.

The scans above that are labeled as experimental are being conducted as a research tool. Safety and efficacy of the scans themselves are not being evaluated. Similarly, when MRI is acquired on the MRI750 model at Waisman or at WIMR, a 32 channel NOVA head coil will be used. This coil is non product and thus experimental. The study is not evaluating the safety or efficacy of the head coil.

Quality review: MRI and PET scans will be checked immediately after acquisition for technical quality (motion and other artifact) of the T1-weighted sequence and if needed this may be rescanned either during the same MRI session or at a rescheduled session. Images are uploaded to the Wisconsin ADRC imaging lab immediately after the session and the post-processing procedures are implemented including an additional quality check by the study team.

7.1.8 Radiology Review of MRI:

All MR images receive radiological review from the MRI Service of our ADRC (Neuroradiologist Howard Rowley or a similarly qualified neuroradiologist) within 30 days, to screen for clinical abnormalities that may not have been previously detected; any significant findings are referred for clinical follow-up.

7.1.9 PiB at Screening:

[^{11}C]PiB is synthesized using our standard methods. N-methylation of the 6-OH-BTA-0 precursor (ABX, Inc.) is accomplished using [C-11]methyl triflate produced via an automated chemistry module and subsequently purified using HPLC. Typical yields of final [C-11]PiB product are in excess of 2 GBq, with specific activities of 150 – 600 GBq/umol.

PiB PET/CT Scanning: Participants are positioned head first, supine with the canthomeatal line parallel to the in-plane field of view. A CT scan is acquired for attenuation correction. A 70 minute dynamic [C-11]PiB PET acquisition is then initiated with the injection of a 15 mCi target dose of [C-11]PiB bolus, injected over 30 s. For participants who may not be able to tolerate this long scan, a 20 minute scan will be offered after 50 minutes of uptake. Dynamic acquisition frames included 5 x 2 min and 12 x 5 min for a total of 17 time frames. The PET data are reconstructed using a filtered back-projection algorithm (DIFT) with sinogram trimming to a voxel size of 2.57mm x 2.57mm x 2.43mm and matrix dimension of 128 x 128 x 63 and corrected for random events, attenuation of annihilation radiation, deadtime, scanner normalization and scatter radiation with attenuation correction. The reconstructed time series PET data are realigned to correct for subject motion during the course of the study and a denoising algorithm is applied to the voxel-based time series (Christian, Vandehey, Floberg, &

Mistretta, 2010; Floberg et al., 2012). The PET time-series is coregistered into the space defined by the T1-weighted MRI scan based upon coregistration with the time-integrated (i.e. sum image) [C-11]PET scan using mutual information.

PiB Distribution volume Ratio Maps: The data are transformed into voxel-wise parametric images representing [C-11]PiB binding using the cerebellar cortex as a reference region of negligible binding (Price et al., 2005). The cerebellar time-activity curve is extracted from the PET data using a cerebellar gray matter (GM) mask image derived from the coregistered T1-weighted MRI using FreeSurfer software. Voxel-based parametric images using Logan graphical analysis are created as described previously (Lopresti et al., 2005). For the Logan graphical method (Logan et al., 1996), linear regression was applied to the transformed data using the 35- to 70-min (7 points) interval and a mean efflux constant of 0.149 min^{-1}. Using SPM12, the DVRs are also spatially normalized to the International Consortium for Brain Mapping 152 atlas (ICBM 152, i.e. MNI space) and smoothed with an 8 mm full width at half maximum Gaussian kernel and entered into voxel-wise group analyses.

The CT component of the PET/CT scan may be repeated up to one time per study timepoint. The CT attenuation correction scan may be repeated if the scan fails for some reason, or if the participant must get off of the scanner bed.

7.1.10 [^{18}F]MK-6240

Descriptive name: 6-Fluoro-3-(1*H*-pyrrolo[2,3-*c*]pyridin-1-yl)isoquinolin-5-amine.

The synthesis and PET/CT scanning with MK6240 will be done consistent with the Investigators Brochure and the IND. F-18 is created with the GE PETrace cyclotron at WIMR. Radiolabeling is performed using automated research chemistry synthesis units for C-11 methylation (Scansys), F-18 nucleophilic substitution (ELIXSYS, Synthera, Scansys, CTI CPCU). Analytic equipment includes HPLC, GC, TLC and Endosafe-PTS for performing radiopharmaceutical quality assurance. For this project, a dedicated HPLC system will be committed to the synthesis of [F-18]MK6240.

A 5 mCi dose ±20% of MK6240 bolus is injected over 30 second infusion at Baseline, 6, 12, and 24 months. If the 6, 12, or 24 month visit is missing, this may also occur at 18 and/or 30 months, totaling a maximum of 4 timepoints. Scanning occurs for up to 40 minutes starting at 70 minutes post-injection. Repeat of up to two [^{18}F]MK-6240 PET imaging scans over the course of the study may be completed if needed, if the patient remains under the annual radiation allowance. Repeat scans will be prioritized for the Baseline and 12 month visits. Scans will be repeated only one time per study timepoint (e.g. the baseline scan would only be repeated up to one time). Scans may be repeated if the participant moves during the scan such that the images aren't useable for analysis, or if the participant can't tolerate the full imaging session such that the required imaging frames aren't acquired. SUVR images will be generated using the inferior cerebellum as the reference region of nondisplaceable uptake.

The SUVR maps will be coregistered to structural T1-weighted MRI images for voxel- and ROI-based analysis. Details about dosimetry are provided in the investigators brochure.

The CT component of the PET/CT scan may be repeated up to one time per study timepoint. The CT attenuation correction scan may be repeated if the scan fails for some reason, or if the participant must get off of the scanner bed.

7.1.11 Data obtained from referral sources:

This study recruits from the Wisconsin ADRC, WRAP and local UW memory clinics, and relevant information pertinent to subject selection and screening will be obtained regarding cognitive diagnosis and medical history.

Data collection from source study and clinical referral source

This study recruits from WRAP and Wisconsin ADRC and local UW memory clinics, and relevant information from those sources may be used to determine eligibility. Information to be collected includes the following:

Diagnosis: From the memory clinics this would include physician summary reports with diagnostic information. From the ADRC and WRAP this would include diagnostic consensus conference summaries and reports. Primary diagnoses (such as MCI or dementia due to AD) and any relevant secondary diagnoses (such as vascular disease) would be captured. Rationale: Diagnosis is a main grouping variable.

Medical history will be accessed as part of the subject selection and screening process. For the clinic this may include the memory clinic physician summaries/notes and for the ADRC/WRAP would include clinician and self-reported medical history survey results. The rationale is to identify people who are eligible.

Prior imaging: Although we will collect an MRI under this protocol, results/reports from prior MRIs conducted for WRAP or ADRC in the past 24 months may be used to guage eligibilty. Rationale: To avoid screening someone whose may be ineligible based on the existing MRI.

Genetics: APOE genetic status will be collected from the ADRC and WRAP source cohorts rather than repeating it.

7.1.12 Discontinuation of Study Treatment and Premature Subject Withdrawal

Subjects who discontinue prior to completing the 12-month or 18 month [^{18}F]MK-6240 PET scan will be eligible for replacement in the study until a total of at least 15 MCI/AD subjects complete the 12 month PET imaging session. Subjects that complete the 12-month visit but wish to abandon the study before the 24-month visit will be given the option to have a final evaluation (including all the original assessments and imaging) any time between 18 and 24 months.

Subjects may voluntarily withdraw from the study for any reason at any time. They will be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs, the study team will make every effort to determine the primary reason for a subject's premature withdrawal from the study and document this information. In addition, the study team will ask the subject to return for an Early Terminations Visit for a final evaluation.

Subjects may develop adverse events or abnormalities in vital signs, physical or neurological examination, or laboratory determinations during their participation in the study. If these occur, the investigator may discontinue a subject from the study if, in his/her clinical judgment, continued participation would result in undue risk or further worsening of the condition.

For subjects who are lost to follow-up (i.e. those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator will show due diligence by documenting attempts to contact the subject, e.g. dates of telephone calls, registered letters, or other attempts to communicate.

7.2 Study Completion

The study will be complete when the last subject (including replacement subjects) completes the final visit and follow up phone call.

7.3 Data Sharing:

Banked images and their meta-data from this study will be managed by the ADRC imaging core and provided to authorized ADRC and WRAP investigators. Images from ADRC participants may be uploaded to the National Alzheimer's Coordinating Center or other NIH-specified repository. The images from applicable subjects will also be shared back with the source protocols and with the ADRC UP protocol (2013-0178) to address the major specific aims of the UP project. Once the data are shared with repositories and with the source protocols, the data may be used to address future unspecified research by WRAP and ADRC investigators. Other investigators who wish to use these data may apply via established resource request mechanisms to the ADRC and WRAP, and the respective executive committees will evaluate the merit of the request and decide how these and other ADRC or WRAP data are shared. Investigators from within the ADRC and WRAP, other departments within UW, institutions outside UW, and private companies may submit applications requesting the data. Only coded data are shared with researchers that are not listed as key personnel on the projects. Dr. Johnson holds ultimate responsibility for data sharing oversight, and will review all requests. He will ensure that local IRB policies are followed prior to releasing data.

Data shared with the study sponsor, Cerveau Technologies, Inc.:

Only data collected under this protocol will be shared with the study sponsor.

-MK-6240 Tau Brain PET Image

-Brain MR Images

-Unique Subject Identifier
-Amyloid image and status
-Cognitive metrics consisting of MMSE, ADAS-COG and CDR
-Weight/Height
-Scan time
-MK-6240 dose
-Scan date
-Clinical diagnosis
-Age, gender, race/ethnicity
-Smoking status

All data shared with Cerveau will be coded by participant ID. Cerveau maintains safety data for all sites using the MK6240 drug, and is responsible for Investigational Drug Brochure updates.

StatKing Clinical Services (TrialMaster)

The Electronic Data Capture (TrialMaster) will be hosted by StatKing Clinical Services, will be used to record all visit data. Data to be recorded include visit dates, dates of informed consent and enrollment, demography, health and smoking history, pregnancy test results if applicable, height/weight, APOE Status, vital signs, cognitive test scores, MRI sequence details, PET scan details, drug dosing details, AEs, concomitant medications, and follow-up call results. TrialMaster is in compliance with 21 CFR Part 11, electronic records, electronic signatures and predicate rules. Compliance is achieved through a combination of SOP adherence and a structured validation system. Security of the EDC system includes the use of passwords that limit user access according to their job responsibilities. Access to the data at the clinical site is restricted to authorized personnel only. Usernames and passwords are sent in two separate emails to personalized email addresses only.

BIOCLINICA

Bioclinica will provide secure storage of the study images and will be responsible for transferring MRI and PET images to the sponsor. Bioclinica will perform study start-up activities, prepare materials and forms which will be used for training and collection of images and perform image data quality control. Bioclinica will also prepare the study procedure manuals to ensure consistent image acquisition and transfer via SMART Submit, Bioclinica' s electronic image submission system. SMART submit is in compliance with 21 CFR Part 11, electronic records, electronic signatures and predicate rules. Compliance is achieved through a combination of SOP adherence and a structured validation system. Security of this system includes the use of passwords that limit user access according to their job responsibilities. In addition, ongoing calibration of PET scanners will be monitored by the collection of quarterly report sheets. Throughout the study an image data back-up will be performed on data storage systems. Off-site image data back-up will also be performed. Other electronic data (electronic CRFs, audit trails, database contents, electronic documents, etc.) will be stored on a dedicated

database server and saved daily throughout the study. Access to the data at the clinical site is restricted to authorized personnel only.

7.4 Data Banking

Data banking is a required component of the study; participants must agree to data banking at the time of consent. Participants may request to have their data withdrawn from the bank, at which point study personnel will remove their data from the bank and will discontinue using it for further research. Data collected from this study will be stored on Department of Medicine computer servers that are password-protected. Banked data is coded with a subject ID. Only study personnel have access to the key linking subject ID and identifiable subject information. Unless staff are listed as key personnel on this study, they will not be given access to the code linking subject identity with subject ID.

8 SAFETY CONSIDERATIONS

8.1 Adverse Events

An **adverse event (AE)** is any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events will be recorded regardless of their relationship to the study.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

Serious adverse events will be reported by the investigator to the Sponsor, FDA, and IRB within the required timeframes after learning of the event.

8.2 Adverse Events and Serious Adverse Events Monitoring

Given that this longitudinal study involves procedures that will occur at 6-12 month intervals and does not include chronic treatment with an investigational agent, adverse events (AEs) and serious adverse events (SAEs) will only be captured during the study visit before and after PiB and MK6240 scans. The participant will receive a phone call within 4 days from the study team for the purpose of ascertaining their wellbeing and information on any adverse events that occur within 24 hours after the scan. If any adverse events are discovered, a clinician will continue to follow up with the participant until resolved.

The PI will be apprised of any adverse events and will report any SAEs experienced in the study to the IRB, FDA and sponsor per the relevant regulations. Although no study related adverse events are expected (based on our past experience), we will examine AEs for study related trends. If needed, we would modify the consent form after consulting with the IRB.

8.3 Follow-up for Adverse Events

The investigator is obliged to follow subjects with AE's until the events have subsided, the conditions are considered medically stable, or the participants are no longer available for follow up. Subjects who discontinue due to adverse events will be treated and followed according to established medical practice.

8.4 Risk benefit discussion for pertinent study procedures

MRI – There are no known biologic risks associated with MRI scanning. Participants will be screened by study staff prior to the scan to verify they do not have any contraindications for MRI. Subjects with the following should not participate in MRI studies: metallic implants, such as prostheses, shrapnel, or aneurysm clips, or persons with electronic implants, such as cardiac pacemakers. The magnetic field generated by the MRI machine can cause a displacement or malfunctioning of these devices. Potential side effects of the scan include headache or anxiety due to claustrophobia and/or noise, and risk of injury due to other unapproved metal being brought into the scanner room. To minimize the level of noise, all subjects will be fitted with disposable earplugs. Communication with the participant is still possible during the scan. In addition, fatigue and physical discomfort due to the length of the scan session are possible. An abbreviated scan sessions consisting of the T1-weighted scan and FLAIR scan is sufficient for fulfilling the MRI component of this protocol.

PET/CT Imaging ([F-18]MK6240 and [C-11]PiB radiotracers) – PET/CT imaging involves exposure to small amounts of ionizing radiation, which has no known or expected harmful effects. No serious adverse effects or concerning trends attributable to the radiopharmaceuticals used in this study have been reported. However, the possibility exists for a rare reaction to any of the substances or procedures to which the subject is exposed. Based on data from 6378 administrations of MK6240, the most commonly occurring adverse events possibly related to injection of MK6240 include headache (occurred in 10 out of 6378 participants, or 0.16%) and dizziness (occurred in 2 out of 6378 participants, or 0.03%). The following occurred in only one participant out of 6378, or 0.02%: abdominal distention (bloating or swelling in the belly area), injection site bruising, arthralgia (joint pain), dysgeusia (altered sense of taste), parosmia (altered sense of smell), insomnia (difficulty falling asleep), and dysuria (discomfort when urinating). All reported adverse events were considered mild in intensity, and resolved shortly after the scan. A PET/CT scanner will be used and a low dose CT transmission scan is acquired for attenuation correction (0.4mSv). The whole body radiation dose of 26.9mSv received by the subjects from PET/CT [F-18]MK6240 (5.9mSv for each of 4 visits is 23.6mSv) and [C-11]PiB (3.3mSv) scans will be below the guidelines established in 21CFR §361.1 for whole body (Annual Limit - 50mSv), active blood forming organs, lens of eye and gonads (5 rad) and target organ (15 rad). Specifics regarding the effective human radiation dosimetry for a subject undergoing [F-18]MK6240 and PiB are provided in the Investigators Brochure for each ligand.
Repeat of up to two [^{18}F]MK-6240 PET imaging scans over the course of the study may be completed if needed, if the patient remains under the annual radiation allowance. Each additional [^{18}F]MK-6240 PET imaging scan would expose the participant to an additional 5.9mSv. Repeat scans will be prioritized for the Baseline and 12 month visits. Scans will be

repeated only one time per study timepoint (e.g. the baseline scan would only be repeated up to one time). The CT component of the PET/CT scan may be repeated up to one time per study timepoint (0.4mSv per additional CT scan).

9 DATA HANDLING AND RECORD KEEPING

9.1 Study Monitoring

9.1.1 Internal Audit and Data Safety Monitoring:

The Study Monitoring Plan describes the strategy, responsibilities, and quality management activities in place to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data, in compliance with applicable laws, regulations, policies, and guidance.

This observational cohort study does not require an external DSMC. The radioligands are delivered in tracer quantities that have no known pharmacological effect. However, as described in the Study Monitoring Plan, the investigator and clinical team will review the AE logs and any Study Monitoring findings to determine if there are trends or side effects that are study related that may warrant changes to the protocol and/or consent form.

9.2 Database Management and Quality Control

9.2.1 Data Collection Forms

The study coordinator works with the participant at the study visit to collect all relevant data. Electronic case report forms will be generated to record the data. Source documents and all participant specific data are stored hard copy in an individual binder.

9.3 Data management tools

9.3.1 CoRRIE – CRM database

Directly identifiable information and indirectly identifiable information (identified by Study ID number) will be stored in CoRRIE.

CoRRIE is a contact database that will be used to record participant contacts, correspondence and scheduling. It is used by all ADRC-linked studies. It is a web-based, electronic database that is password-protected.

In addition to storing the names of those who enroll in this study, the CoRRIE database will also help the staff to manage their contacts with participants. The database allows for the storage of participants' relationship to our program by stating which studies in our program they are enrolled in or have been enrolled in the past. The database also allows us to track and assign activities that take place during the course of research (phone calls, letters, screenings).

This helps to ensure that participants are not needlessly contacted, and overall improves the customer service provided to our participants by the members of our research program. The purpose of storing this data is for programmatic cohesion in working with subjects with memory problems across our program. It is important to know which subjects are enrolled in which studies so that we may provide appropriate coordination of their study visits.

Universal Identifier
An internal ID number is generated by the ADRC CoRRIE database and will have "RMRaic00" added to it to create a unique participant identifier that will remain with the participant from study to study. This number will be used to label brain images collected in affiliated ADRC protocols. This will allow physicians who are reviewing the brain scans to look for brain changes over time.

9.3.2 PANDA and PACS

Image data management tool: Image data are electronically transferred and stored on servers at the ADRC imaging core (PI is Dr. Johnson) and metadata inserted into an imaging database called PANDA. Image headers by protocol do not contain identifying information. Additionally, each image is automatically inspected, and any PHI removed. These resources are maintained by the Department of Medicine. Some derived numeric image data, cognitive and questionnaire data may be maintained in PANDA. User access is protocol specific such that only users authorized to see this study's data will have access.

MRI images labeled with only study IDs as identifiers are also uploaded to the Dept of Radiology PACS directly from the scanner for radiology over-reads.

9.3.3 BOOKED:

Directly identifiable information and indirectly identifiable information (identified by Study ID number) will be stored in Booked. A participant scheduling web application, Booked, has been developed by extending the Booked (PHP) free, open source project. The Booked application can prevent double booking of staff and resources, provides email notification to staff when they are added to appointments, provides email notification if an appointment has been cancelled, and email reminders before an appointment starts. Staff can be linked to multiple roles in appointments. The calendar view can be filtered by resource, staff and study participant. The appointments are color coded by appointment type and staff member. Booked reports can track cancelled appointments, cancellation reason, appointment types, resource usage, staff hour totals, and staff appointment counts. Booked is limited to https ssl connections. Only users granted protocol specific permissions can login to Booked and view study participant information. It is also important to note that the Booked software is installed on the DOM production server in the DOM server room; therefore, all Booked data will be on the DOM server. Access to Booked via the web is limited to UW Networks. Booked is a free, open source project; therefore, there are no connections or relationships with the Booked software manufacturer. Participant Name, phone number and ADRC Registry ID (2016-0735) are identifiers used in Booked. Booked is an appointment scheduling application, so the

participant name, phone and Study ID are needed to identify the participant. These identifiers will only be visible to users who are on the protocols that the participant is enrolled in.

10 STATISTICAL CONSIDERATIONS

10.1 Subject Demographics and Other Baseline Characteristics

The demographic and baseline characteristics will be summarized according to the clinical group (HV, MCI, mild or moderate AD) using descriptive statistics for continuous variables and using frequency count and percentage for discrete variables.

10.2 Image Analysis

The MRI and [^{18}F]MK-6240 PET images will be co-registered for anatomy-based definition of regions of interest (ROI) for analysis of regional [^{18}F]MK-6240 binding/uptake. The [^{18}F]MK-6240 PET analysis will include application of spatially standardized region of interest (ROI) templates to assess tracer uptake and quantification. Standard uptake values (SUV) and Standardized Uptake Value Ratios (SUVR) will be calculated for the areas and will serve as the primary imaging outcome measure.

10.3 Statistical Analysis

Descriptive statistics will be used to describe the tau deposition (e.g. composite and regional SUVR, voxel based statistics or change in tau distribution) using [^{18}F]MK-6240 PET.

The Baseline [^{18}F]MK-6240 binding will be compared among the AD subjects at different stages of the disease, and HV groups descriptively, quantitatively and visually by graphical plots. [^{18}F]MK-6240 binding in AD at different stages of the disease, and HV binding across multiple regions will be compared. Within the AD groups, the distribution and binding of [^{11}C]PiB will be compared to the [^{18}F]MK-6240 binding across multiple regions.

The primary objective of this imaging trial is to evaluate the longitudinal change in [^{18}F]MK-6240. Composite and regional SUVRs will be determined for each of the [^{18}F]MK-6240 imaging sessions (Baseline, 6-month, 12-month, and 24-month). This may also include 78 (18 month) and/or 130 (30 month) week measures, if the 26, 52, or 104 week measures are not available in order to assess change over intervals of 6, 12, 18 and 24 months. The analysis will include, but not be limited to, the following regions of interest: inferolateral temporal cortex, posterior cingulate, frontal cortex, parietal cortex, occipital cortex, mesial temporal cortex and anterior cingulate. To help control type 1, a composite inferomedial region will be used as the primary outcome. Change in tau regional deposition and/or volume of deposition as measured by [^{18}F]MK-6240 (e.g. composite and regional SUVR, voxel based statistics or change in tau distribution) will be determined by estimating the change from baseline to each follow-up visit using an appropriate repeated measures metric. The change in tau burden will be compared among the groups (HV, prodromal, mild and moderate AD).

The relationship between the change in tau deposition by [^{18}F]MK-6240 (e.g. composite and regional SUVR, voxel based statistics or change in tau distribution) and change in clinical

biomarker measures will be examined in prodromal, mild and moderate AD subjects. In addition, the correlation between baseline tau burden and AD severity based on clinical scales, venous blood biomarkers in prodromal, mild and moderate AD subjects will be evaluated.

10.4 Sample Size

The sample size for this study was determined by practical considerations and is not based on statistical power calculations. Up to 42 subjects maybe enroll in this study or no less than 15 MCI/mild AD subject, 3 moderate AD subjects and 5 similarly aged healthy volunteers all with a least the 12 month scan.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the University of Wisconsin-Madison Health Sciences IRB.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record. Only participants with cognitive capacity to provide consent will enroll in this study.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, MRI and PET images, and other records will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

Privacy and Data Storage

Physical data will be kept in locked cabinets in our lab which has space at the UW Hospital. Other data will be kept on the Department of Medicine's secure server. Only individuals in our lab will have access to these computers and any PHI. Any data shared with individuals outside of our lab (i.e. papers or presentations) will be anonymized. Each subject will also have an individual study number to code their study data. Names are never entered at the scanner console, only study number. Study number is used on data collection forms.

Directly identifiable information and indirectly identifiable (identified by study ID number) information will be stored in CoRRIE and Booked.

CoRRIE is an electronic database/contact management system that stores information (inclusive of PHI) from the 'First Contact Form' as described in 2016-0735 and tracks study participation. The electronic database is web-based, though only accessible within the DOM server, and password-protected. Data are not stored in temporary files. Registered accounts must be approved by our research staff supervisors, and access/activity in the database will be monitored. Only those listed on the 2016-0735 protocol will be allowed access. Data will be kept in a web-based electronic database stored on the DOM server, with access only allowed to authorized research personnel.

Booked is a participant visit scheduling web application that has been developed by extending the Booked (PHP) free, open source project. Booked software has been installed on the DOM production server in the DOM server room. All Booked data will be on the DOM server. Access to Booked via the web is limited to UW DOM Networks. Booked is a free, open source project; therefore, there are no connections or relationships with the Booked software manufacturer and data will not be stored online with the software manufacturer. Booked is limited to https ssl connections. Only users granted protocol specific permissions can log in to Booked and view study participant information. Booked is an appointment scheduling application, so the participant name, phone number, and Registry ID are needed to identify the participant. These identifiers will only be visible to users who are on the protocols which the participant is enrolled in. The DOM IT department has been consulted with regard to HIPAA security requirements.

PANDA (PAN = Greek prefix meaning ‘all’; Data Archive) is a data and imaging management tool that has received IRB approval for use in other ADRC and WRAP linked protocols. Data and images are electronically transferred to PANDA, which is maintained by the ADRC imaging core. The PANDA is a Ruby on Rails application using a MySQL backend database, which provides secure web interfaces to a repository of MRI, PET and project-specific variables including neuropsychology, lab results, questionnaires, and participant properties. Security of the database uses best practice guidelines. Viewing and editing data are separately granted permissions and are access-controlled at the project level. Editing of data will be locked to all but the DBA. In all cases this also requires a user to be listed on the IRB-approved protocol (via ARROW study team list). For security, all login and query downloads are logged and traceable by user and date. Further, any logged query, including table fields and selection criteria, may be reconstructed at a later date for auditing if needed. The DBA has an interface to view the queries by user/time. As imaging data cannot be uploaded, it is the image metadata that are uploaded into the SQL database; the images themselves are stored on a secure DOM server in the imaging core. Data are transferred to database users using https downloads of queries in CSV text files that can subsequently be imported into statistical analysis software.

11.4 Study Discontinuation

The study may be discontinued at any time by the investigator, the IRB, the sponsor, or by regulatory agencies including the FDA as part of their duties to ensure that research

participants are protected.

12 CLINICALTRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify participants of this study. At most, the website will include a summary of the results.

13 REFERENCES

Betthauser, T. J., Cody, K. A., Zammit, M. D., Murali, D., Converse, A. K., Barnhart, T. E., Stone, C. K., Rowley, H. A., Johnson, S. C., & Christian, B. T. (2018). In vivo characterization and quantification of neurofibrillary tau PET radioligand [F18]MK-6240 in humans from Alzheimer's disease dementia to young controls. *Journal of Nuclear Medicine, in press*. doi:10.1101/290064

Braak, H., & Braak, E. (1990). Neurofibrillary changes confined to the entorhinal region and an abundance of cortical amyloid in cases of presenile and senile dementia. *Acta Neuropathol (Berl), 80*(5), 479-486.

Braak, H., Braak, E., & Bohl, J. (1993). Staging of Alzheimer-related cortical destruction. *European Neurology, 33*(6), 403-408.

Chien, D. T., Szardenings, A. K., Bahri, S., Walsh, J. C., Mu, F., Xia, C., Shankle, W. R., Lerner, A. J., Su, M. Y., Elizarov, A., & Kolb, H. C. (2014). Early clinical PET imaging results with the novel PHF-tau radioligand [F18]-T808. *J Alzheimers Dis, 38*(1), 171-184. doi:10.3233/JAD-130098

Christian, B. T., Vandehey, N. T., Floberg, J. M., & Mistretta, C. A. (2010). Dynamic PET denoising with HYPR processing. *J Nucl Med, 51*(7), 1147-1154. doi:10.2967/jnumed.109.073999

Floberg, J. M., Mistretta, C. A., Weichert, J. P., Hall, L. T., Holden, J. E., & Christian, B. T. (2012). Improved kinetic analysis of dynamic PET data with optimized HYPR-LR. *Med Phys, 39*(6), 3319-3331. doi:10.1118/1.4718669

Gomez-Isla, T., Price, J. L., McKeel, D. W., Jr., Morris, J. C., Growdon, J. H., & Hyman, B. T. (1996). Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. *J Neurosci, 16*(14), 4491-4500.

Hostetler, E. D., Walji, A. M., Zeng, Z., Miller, P., Bennacef, I., Salinas, C., Connolly, B., Gantert, L., Haley, H., Holahan, M., Purcell, M., Riffel, K., Lohith, T. G., Coleman, P., Soriano, A., Ogawa, A., Xu, S., Zhang, X., Joshi, E., Della Rocca, J., Hesk, D., Schenk, D. J., & Evelhoch, J. L. (2016). Preclinical Characterization of 18F-MK-6240, a Promising PET Tracer for In Vivo Quantification of Human Neurofibrillary Tangles. *J Nucl Med, 57*(10), 1599-1606. doi:10.2967/jnumed.115.171678

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E., Snyder, H. M., Sperling, R., & Contributors. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement, 14*(4), 535-562. doi:10.1016/j.jalz.2018.02.018

Johnson, S. C. (2018). Brain imaging in dementia and antecedent conditions. In G. E. Smith (Ed.), *APA Handbook of Dementia*. Washington D. C.: APA.

Logan, J., Fowler, J. S., Volkow, N. D., Wang, G. J., Ding, Y. S., & Alexoff, D. L. (1996). Distribution volume ratios without blood sampling from graphical analysis of PET data. *J Cereb Blood Flow Metab, 16*(5), 834-840. doi:10.1097/00004647-199609000-00008

Lohith, T. G., Bennacef, I., Vandenberghe, R., Vandenbulcke, M., Salinas-Valenzuela, C., Declercq, R., Reynders, T., Telan-Choing, F., Riffel, K., Celen, S., Serdons, K., Bormans, G., Tsai, K., Walji, A., Hostetler, E. D., Evelhoch, J. L., Van Laere, K., Forman, M., Stoch, A., Sur, C., & Struyk, A. (2018). First-in-human brain imaging of Alzheimer dementia patients and elderly

controls with (18)F-MK-6240, a PET tracer targeting neurofibrillary tangle pathology. *J Nucl Med*. doi:10.2967/jnumed.118.208215

Lopresti, B. J., Klunk, W. E., Mathis, C. A., Hoge, J. A., Ziolko, S. K., Lu, X., Meltzer, C. C., Schimmel, K., Tsopelas, N. D., DeKosky, S. T., & Price, J. C. (2005). Simplified quantification of Pittsburgh Compound B amyloid imaging PET studies: a comparative analysis. *J Nucl Med, 46*(12), 1959-1972. doi:46/12/1959 [pii]

Maruyama, M., Shimada, H., Suhara, T., Shinotoh, H., Ji, B., Maeda, J., Zhang, M. R., Trojanowski, J. Q., Lee, V. M., Ono, M., Masamoto, K., Takano, H., Sahara, N., Iwata, N., Okamura, N., Furumoto, S., Kudo, Y., Chang, Q., Saido, T. C., Takashima, A., Lewis, J., Jang, M. K., Aoki, I., Ito, H., & Higuchi, M. (2013). Imaging of tau pathology in a tauopathy mouse model and in Alzheimer patients compared to normal controls. *Neuron, 79*(6), 1094-1108. doi:10.1016/j.neuron.2013.07.037

Mattsson, N., Andreasson, U., Persson, S., Carrillo, M. C., Collins, S., Chalbot, S., Cutler, N., Dufour-Rainfray, D., Fagan, A. M., Heegaard, N. H., Robin Hsiung, G. Y., Hyman, B., Iqbal, K., Lachno, D. R., Lleo, A., Lewczuk, P., Molinuevo, J. L., Parchi, P., Regeniter, A., Rissman, R., Rosenmann, H., Sancesario, G., Schroder, J., Shaw, L. M., Teunissen, C. E., Trojanowski, J. Q., Vanderstichele, H., Vandijck, M., Verbeek, M. M., Zetterberg, H., Blennow, K., Kaser, S. A., & Alzheimer's Association, Q. C. P. W. G. (2013). CSF biomarker variability in the Alzheimer's Association quality control program. *Alzheimers Dement, 9*(3), 251-261. doi:10.1016/j.jalz.2013.01.010

Price, J. C., Klunk, W. E., Lopresti, B. J., Lu, X., Hoge, J. A., Ziolko, S. K., Holt, D. P., Meltzer, C. C., Dekosky, S. T., & Mathis, C. A. (2005). Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh Compound-B. *J Cereb Blood Flow Metab, 25*(11), 1528-1547.

Villemagne, V. L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K. A., Salvado, O., Szoeke, C., Macaulay, S. L., Martins, R., Maruff, P., Ames, D., Rowe, C. C., Masters, C. L., & Australian Imaging Biomarkers Lifestyle Research Group. (2013). Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol, 12*(4), 357-367. doi:10.1016/S1474-4422(13)70044-9

Villemagne, V. L., Furumoto, S., Fodero-Tavoletti, M. T., Mulligan, R. S., Hodges, J., Harada, R., Yates, P., Piguet, O., Pejoska, S., Dore, V., Yanai, K., Masters, C. L., Kudo, Y., Rowe, C. C., & Okamura, N. (2014). In vivo evaluation of a novel tau imaging tracer for Alzheimer's disease. *Eur J Nucl Med Mol Imaging, 41*(5), 816-826. doi:10.1007/s00259-013-2681-7

Villemagne, V. L., Mulligan, R. S., Pejoska, S., Ong, K., Jones, G., O'Keefe, G., Chan, J. G., Young, K., Tochon-Danguy, H., Masters, C. L., & Rowe, C. C. (2012). Comparison of 11C-PiB and 18F-florbetaben for Abeta imaging in ageing and Alzheimer's disease. *Eur J Nucl Med Mol Imaging, 39*(6), 983-989. doi:10.1007/s00259-012-2088-x