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

Protocol ID: ALERTT

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Statistical Analysis Plan

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1 PROTOCOL SYNOPSIS (FROM PROTOCOL)

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). • 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. • To evaluate cross-sectional comparison of [^{18}F]MK-6240 uptake in AD, MCI and HV at baseline 26, 52 and 104 weeks
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 (14 MCI/mild AD, 3 moderate AD, 6 HV subjects) to complete the 24 month follow up. Subjects who discontinue prior to completing the 12-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 (or their legal authorized representative when applicable) will provide informed consent 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. [^{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. [^{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 120 minutes post-injection. 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 or the subject's legally authorized representative or caregiver (if applicable) 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, agrees to accompany the subject and provide information at visits, and signs the necessary consent form. 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)

- Subject has received an investigational drug or device within 30 days of screening.
- 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 24-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.
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 month study.
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). The change in [^{18}F]MK-6240 uptake will be compared among the groups (AD, MCI and HV subjects). 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.

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 et al., 1993). However, the rate of temporal change in neurofibrillary tangle burden in individual cases is poorly understood. 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.

[^{18}F]MK-6240 has been previously evaluated by several groups including ours (Betthauser et al., 2018) 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.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objectives of this study is:

- To estimate rates of 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).
- To correlate the changes in [^{18}F]MK-6240 uptake and changes in clinical cognitive assessments (MMSE, ADAS-cog and CDR).

3.2 Secondary Objectives

The secondary objectives of this study are:

- To estimate rates of 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.
- To evaluate cross-sectional comparison of [^{18}F]MK-6240 uptake in AD, MCI and HV at baseline 26, 52 and 104 weeks

4 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**.

5 STATISTICAL ANALYSIS PLAN

5.1 Image Pre-processing

The MRI, PiB 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 PET analyses will include application of spatially standardized region of interest (ROI) templates to assess tracer uptake and quantification. Standardized Uptake Value Ratios (SUVR) will be calculated as described by Betthauser et al 2018 and ROIs extracted that represent Braak and Braak staging.

Tau Braak and Braak stage equivalent regions of interest using the Harvard Oxford Brain atlas for defining regions of interest bilaterally:

Stage I: entorhinal cortex average SUVR

Stage II: Hippocampus and amygdala average SUVR

Stage III: fusiform average SUVR

Stage IV: Inferior temporal and middle temporal gyrus average SUVR

Stage V: Superior temporal gyrus average SUVR

Stage VI: Cuneus and pericalcarine cortex average SUVR

Amyloid load:

PIB Index: is comprised of the average signal extracted from the DVR image of eight bilateral ROIs including the anterior cingulate, posterior cingulate, precuneus, angular gyrus, supramarginal gyrus, superior temporal gyrus, middle temporal gyrus, medial orbital gyrus.

Visual rating: As described in Johnson et al 2014 a rating of elevated, not elevated or indeterminate is assessed for each amyloid scan.

MRI:

Hippocampal volume: obtained using FIRST/FSL and adjusted for total intracranial volume using a regression approach.

Total atrophy: expressed as a ratio of the volume of segmented CSF to the volume of segmented brain (gray + white matter).

5.2 Descriptive Statistics:

General approach: Because the sample sizes are small, and because the goal of the project is to characterize rates of change by clinical status, the objectives of the analyses are largely descriptive in nature.

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. Plots of relevant variables will be examined for skewness and transformed as necessary prior to any analyses.
Descriptive statistics and counts (with histograms when relevant) will be ascertained for the following variables by diagnostic group:
Age, sex, education, race/ethnicity; ADAS-Cog total score and ADAS-Cog13 subscore, MMSE score; CDR-sum and weighted scores; Amyloid status and PIB index score; MK6240 estimated Braak stage and SUVR values for each of six regions of interest representing each Braak Stage; hippocampal volume (corrected for total intracranial volume) and estimate whole brain atrophy (CSF volume to brain volume).

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. A primary region of interest will be comprised of the average signal in the entorhinal cortex, amygdala, hippocampus, and anterior fusiform gyrus [^{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.

Cross-sectional Spearman correlations will be computed by group at Baseline, 6, 12 and 24 months for the following measures: [^{18}F]MK-6240 uptake neuropsychological testing (MMSE, CDR-SB, ADAS-cog), hippocampal volume and whole brain atrophy.

5.3 Longitudinal Analysis

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) in the six specific regions (approximating Braak stages) as described above. Change in tau regional deposition as measured by [^{18}F]MK-6240 will be determined by estimating the mean change from baseline to each follow-up visit for each ROI by diagnostic group. The mean change and standard deviation will be computed for each region and group. These regional means and SDs by region and group are the primary objectives of the project. The Kruskal-Wallis test will be performed to determine if rates of change differ by group.

The relationship between the change in tau deposition by [^{18}F]MK-6240 and baseline PIB status will be assessed with Spearman correlation.

5.4 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.

5.5 ENDPOINTS

The primary endpoint is change in MK6240 binding from baseline to 12 months in a composite region comprising the entorhinal cortex, amygdala, hippocampus and anterior fusiform. The secondary enpoints include 6 and 24 month change.

5.6 MISSING VALUES

Missing values in a longitudinal study of persons with dementia is expected. A closeout visit will be completed when possible. Imputation methods will be utilized and missingness will be assumed to be ‘not random’.

5.7 QC PLANS

Image Data:

The principal investigator has oversight of image quality at the institution as established in the protocol and technical documents including the PET Imaging Manual, MR Imaging Manual, Image Charter and Data Transfer Specifications. The operations of the image core as hosted by Bioclinica will be conducted in accordance with Bioclinica’s standard operating procedures in accordance with the clinical protocol and technical documents. All image data will be submitted to the image core online through SMART Submitt as hosted by Bioclinica. The final database will be provided to the institution in accordance with the Data Transfer Specification.

Clinical Data:

All data will be submitted through the internet via the electronic data capture system hosted by Statking Clinical Services. Data for this study will be entered and accepted from the site into TrialMaster, a 21 CFR 11 compliant system in accordance with the User Completion Guidelines and managed by Statking Clinical Services in accordance with the Data Management Plan and

Statking Clinical Services SOPs. The electronic database will be locked upon completion of the last iCRFs, the last resolved query and the completion of the QC of the data. After the electronic database has been locked, per SCS's SOPs, the final study database will be provided to the institution in accordance with the Data Transfer Plan.

The institution will conduct quality oversight of all trial data in accordance with the monitoring plan perform quality control and quality assurance checks on the clinical study data.

5.8 PROGRAMMING PLANS

Statistics will be programmed in R and scripts will be made available for inspection/input and use by study sponsors and other stake holders.

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