ALZHEIMER'S PET IMAGING IN RACIALLY/ETHNICALLY DIVERSE ADULTS

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Study Product: *^{18}F-MK-6240*
^{18}F-Neuraceq, ^{18}F-Florbetaben

NCT number: *NCT03706261*

IND Number: 140399

Protocol Date: July 29, 2022

CONFIDENTIAL

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List of Abbreviations

PET	Positron Emission Tomography
AD	Alzheimer's disease
MRI	Magnetic resonance imaging
^{18}F	Flourine-18
MK-6240	6-Fluoro-3-(1*H*-pyrrolol[2,3-*c*]pyridine-1-yl)isoquinolin-5-amine
Florbetaben	4-[(E)-2-(4-{2-[2-(2-[18F] fluoroethoxy) ethoxy] ethoxy} phenyl)vinyl]-N-methylaniline
CVD	Cerebrovascular disease
IV	intravenous
Ci	Curie
Bq	Becquerel
SUV	Standard uptake value
SUVR	Standard uptake value ratio
Aβ+	Amyloid positivity
FDA	Federal Drug Administration
BBB	Blood-brain barrier
NFT	Neurofibrillary tangle
V_T	Volume of distribution
M	Molar
w/v	Weight by volume
v/v	Volume by volume
NOAEL	No-observed-adverse-effect-level
^{3}H	Tritium
K_d	Equilibrium dissociation constant
FTD	Frontotemporal dementia
ICH	International Conference on Harmonization
MNI	Molecular NeuroImaging
AE	Adverse events
VOI	Volumes of interest
BP_{ND}	Binding potential
HV	Healthy volunteer
DVR	Distribution volume ratio
SoT	Standard of Truth
BSS	Bielschowsky silver staining
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
DLB	Dementia with Lewy bodies
ECG	Electrocardiogram
SAE	Serious adverse event
ECI	Extracorporeal irradiation
CT	Computed tomography
ED	Effective dose
Sv	Sievert
Gy	Gray

FOV	Field of view
MPRAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
ROI	Region of interest
FS	FreeSurfer
CRF	Case report form
UP	Unexpected problem
HIPAA	Health Insurance Portability and Accountability Act
PHI	Protected health information

Study Summary

Title	Alzheimer's PET Imaging in Racially/Ethnically Diverse Adults
Short Title	Alzheimer's PET Imaging in Racially/Ethnically Diverse Adults
Protocol Number	AAAR8986
Phase	I
Methodology	This is a single center PET Study. Racially/ethnically diverse subjects with or without a positive family history of Alzheimer's disease (AD) will have one PET scan with ^{18}F-MK-6240 over a 30 to 60-minute scanning period, and one PET scan with ^{18}F-Florbetaben over a 20-minute scanning period.
Study Duration	5 years
Study Center(s)	Kreitchman PET Center
Objectives	The purpose of this study is to examine the extent to which tau deposition is related to cognitive function, to determine whether tau deposition varies across racial/ethnic groups, to determine the extent to which cerebrovascular disease (CVD) is associated with tau pathology, and to determine if any of those associations depend on amyloid status.
Number of Subjects	150
Diagnosis and Main Inclusion Criteria	Inclusion criteria: • Aged 35 – 85 years • Have either mild cognitive impairment or mild clinical Alzheimer's disease; or have no problem with memory or thinking. • Able to participate in all scheduled evaluations and to complete all required tests and procedures • Considered likely to comply with the study protocol and to have a high probability of completing the study Exclusion criteria: • Past or present history of a certain brain disease other than mild cognitive impairment or mild clinical Alzheimer's disease. • Certain significant medical conditions. Examples are uncontrolled epilepsy or multiple serious injuries.

Diagnosis and Main Inclusion Criteria	• Unable to lie still for PET scans. • Radiation exposure for research studies in the last year that would put you past allowable limits if included in this study. • Participation in the last year in a clinical trial for a disease modifying drug for AD unless it can be determined that your received placebo and not active drug. • Conditions that preclude entry into the scanner (e.g. claustrophobia, etc.). • Inability to have a catheter in your vein for the injection of the radioligand (dye). • Currently pregnant or breastfeeding.
Study Product, Dose, Route, Regimen	^{18}F-MK-6240, 5 mCi, intravenous (IV), one injection ^{18}F-Florbetaben, 8.1 mCi, intravenous (IV), one injection
Duration of administration	A single dose of ^{18}F-MK-6240, the scan takes approximately 30-60 minutes. A single dose of ^{18}F-Florbetaben, the scan takes approximately 20 minutes.
Reference therapy	N/A
Statistical Methodology	The primary outcome measure with be regional standardized uptake value ratio (SUVR) for ^{18}F-MK-6240 and amyloid positivity (Aβ+) for ^{18}F-Florbetaben.

Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization (ICH) guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Alzheimer's disease (AD) is one of the most serious public health crises in modern times that disproportionately affects ethnic and racial minorities[1, 2]. There are currently no effective disease-modifying treatments or preventative strategies. Single pathway pathogenic models emphasize a temporal series of biological changes that drives the neurodegeneration associated with the AD clinical syndrome. The formation of amyloid plaques is thought to initiate the disease, which stimulates intracellular tau pathology, neurodegeneration, and, ultimately, cognitive and functional decline[3, 4]. However, it is now clear that tau deposition often occurs prior to or independent of the formation of amyloid pathology[5-9] and an emerging literature suggests that other factors, including cerebrovascular disease, may potentiate tau pathology[10-12]. After several unsuccessful trials that focus on clearance or prevention of amyloid deposition to treat AD[13, 14], attention is turning towards tau as a more viable treatment target[15], partially due to its tighter link with the clinical symptoms of the disease[16]. It is also becoming clearer that treatment and preventative strategies for AD will be most effective during midlife, before the onset of frank symptomatology[17], consistent with recent mandates to study AD risk factors across the adult lifespan[18]. However, there is very little available information on AD biomarkers during midlife and there is an absolute dearth of existing data on biomarker profiles, their cognitive correlates, and their risk factors among middle-aged ethnic and racial minorities, who are at greater risk for the disease[1, 19].

1.2 Investigational Agent

^{18}F-MK-6240 (6-Fluoro-3-(1*H*-pyrrolo[2,3-*c*]pyridin-1-yl)isoquinolin-5-amine, ^{18}F-MNI-946) is a PET radioligand that binds to paired helical filament tau aggregates. This radioligand has only been used for research purposes. ^{18}F-MK-6240 will be administered in tracer doses at activity of up to 5 mCi (185 MBq) per injection.

^{18}F-Florbetaben (4-[(E)-2-(4-{2-[2-(2-[^{18}F] fluoroethoxy) ethoxy] ethoxy} phenyl)vinyl]-N-methylaniline) is approved and indicated for PET imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.

1.3 Preclinical Data

PET studies in rhesus monkey show that ^{18}F-MK-6240 rapidly crosses the blood-brain barrier (BBB) followed by rapid clearance (Figure 1). Distribution is homogeneous across all brain regions, as expected since neurofibrillary tangle (NFT) pathology is not present in monkey brain (Figure 2). The lack of elevated ^{18}F-MK-6240 retention in white matter compared to gray matter is an important characteristic for a NFT tracer that is not achieved by more lipophilic tracer

compounds. The distribution volume (V_T) in brain stabilized after 60 minutes, indicating influence from radio-metabolites on brain signal is minimal or negligible.

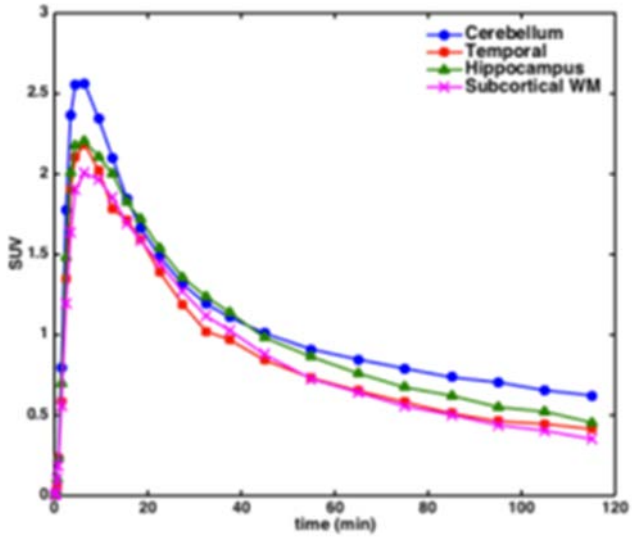


Figure 1. Time-activity Curves for ^{18}F-MK-6240 in Rhesus Monkey.

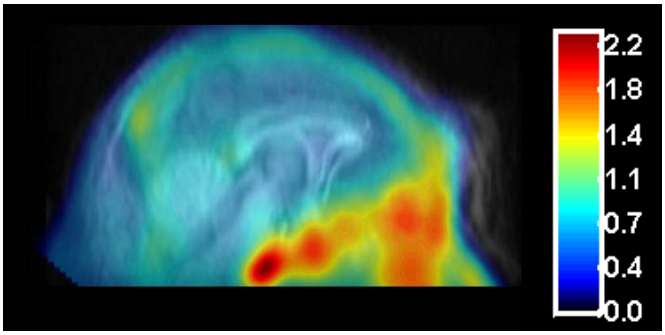


Figure 2. ^{18}F-MK-6240 Summed PET Image (60-120 min) Overlaid on MRI in Rhesus Monkey. Sagittal view; scale is in standard uptake value.

Self-block PET studies (n=3) with ^{18}F-MK-6240 were performed by injecting a high dose of unlabeled MK-6240 prior to radiotracer injection. No significant changes in V_T with respect to baseline were observed (Figure 3) across different brain regions. Additionally, V_T was homogeneous across different brain regions, demonstrating the lack of specific ^{18}F-MK-6240 binding, as expected in the healthy rhesus brain. The corresponding summed PET images from these studies are shown in Figure 4.

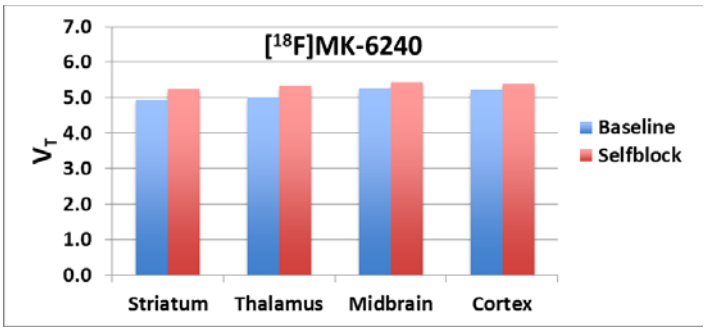


Figure 3. Comparison of V_T in Selected Brain Regions Between Baseline and Self-block PET Studies for ^{18}F-MK-6240.

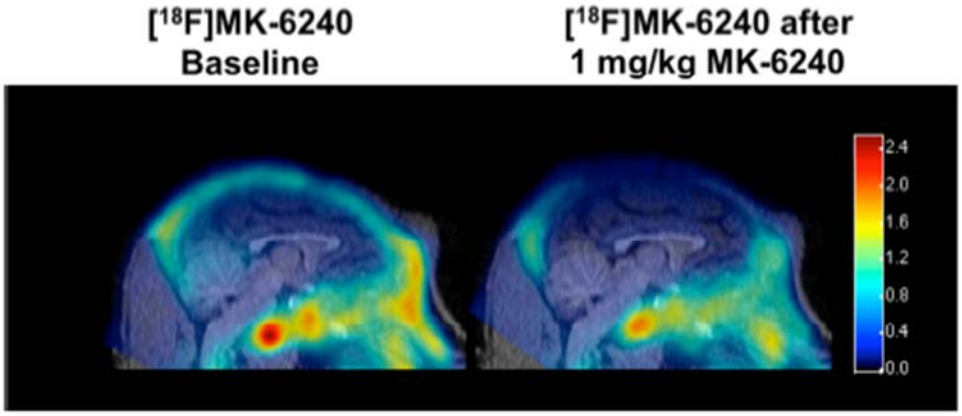


Figure 4. Summed ^{18}F-MK-6240 PET Images (60-120 min) Overlaid on MRI in Rhesus Monkey. Comparison of the Baseline image (left) with the Self-block image (right). Images are representative of results in three different monkeys.

A study was done to determine the potential toxicity of MK-6240 when administered IV (via bolus injection) once daily to rats for 7 or 8 days.

Crl:WI(Han) rats were assigned to 4 groups of 10 females and 10 males each that received 16.6, 33.3, or 333 µg/kg/day of MK-6240 (hydrochloride salt) in 10 mM acetate buffer, 10% (w/v) Captisol™, 0.675% (w/v) sodium chloride, 10% (v/v) ethanol, pH 4, or vehicle only, at a dose volume of 5 mL/kg. The dosing formulations contained the clinical precursor-related impurity at a MK-6240 to impurity ratio of approximately 10:2. Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations.

There were no unscheduled deaths, no MK-6240-related clinical signs, and no changes in body weight or food consumption. There were no changes in hematological, coagulation, serum biochemical examinations or urinalyses, ophthalmic findings, and organ weight changes. There were no gross observations or histomorphologic findings, and no MK-6240-related localized effects observed at the injection sites.

Histomorphologic changes attributable to the administration of Captisol™ were seen in all groups, including control with a comparable incidence and severity (very slight) in the kidneys and in the lungs. They consisted of, in the renal cortex, a fine clear vacuolation of the epithelial cells lining the proximal tubules in females and males and, in the lung, an accumulation of macrophages in the alveoli with occasionally finely vacuolated cytoplasm in males. Similar histomorphologic changes have been seen in rats treated with Captisol™ at this concentration. Therefore, such observations were considered unrelated to the administration of MK-6240. Based on these findings, the no-observed-adverse-effect-level (NOAEL) was ≥333 µg/kg/day.

^{3}H-Florbetaben in vitro binding experiments reveal two binding sites (K_d of 16 nM and 135 nM) in frontal cortex homogenates from patients with AD. Binding of ^{18}F-florbetaben to β-amyloid plaques in post-mortem brain sections from patients with AD using autoradiography correlates with both immunohistochemical and Bielschowsky silver stains. ^{18}F-Florbetaben does not bind to tau or α-synuclein in tissue from patients with AD. Neither Florbetaben nor non-radioactive ^{19}F-florbetaben bind to AT8 positive tau deposits in brain tissue from patients with frontotemporal dementia (FTD), using autoradiography and immunohistochemistry, respectively.

1.4 Clinical Data to Date

MK-6240 was administered at microdoses in accordance with ICH M3(R2) guidelines for an exploratory clinical PET trial. In the three elderly healthy volunteers that were included in the ongoing brain imaging study, after ^{18}F-MK-6240 injection, the radiotracer uptake in brain was high with a peak SUV of ~5, followed by a quick washout from all brain regions. The radioactivity distribution in brain was homogenous across regions including gray and white matter as expected for a healthy volunteer with no NFTs (Figure 5). Absolute quantification of target density in terms of V_T was low, consistent with low potential for non-specific, off-target (non-NFT) binding.

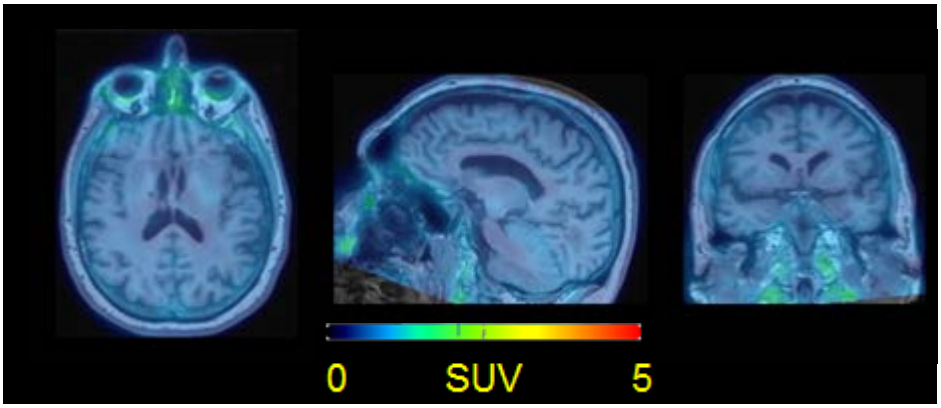


Figure 5. Average PET Image (60 – 90 min) Overlaid on MRI from a 68 Year Old Healthy Male Subject Injected with 155 MBq of ^{18}F-MK-6240.
The color scale for PET image is shown in terms of standardized uptake value (SUV) that is normalized to injected radioactivity and body weight.

In this Phase 0 imaging trial performed by Molecular NeuroImaging (MNI), ^{18}F-MK-6240 (referred to as ^{18}F-MNI-946 in the MNI report) was used for evaluation as a PET radioligand for imaging tau protein deposition, six subjects (3 AD, 3 healthy volunteers) completed the study.

Each subject received one PET scan with ^{18}F-MK-6240. Prior to ^{18}F-MK-6240 each subject underwent a ^{18}F-florbetapir PET screening scan for amyloid deposition. The investigational radiopharmaceutical, ^{18}F-MK-6240, and imaging procedures were well tolerated with no reported adverse events (AEs) related to the product.

Dynamic PET scans were acquired on a Siemens ECAT EXACT HR+ over 180 minutes following ^{18}F-MK-6240 injection (0-90 and 120-180 minute imaging segments). A brain MRI was obtained as part of the screening visit. PET and MRI images were aligned and normalized into the Montreal Neurological Institute space, and ATLAS-based (Hammers, N30R83) volumes of interest (VOI) were applied to the dynamic PET series. ^{18}F-MK-6240 was evaluated in terms of kinetic profile (uptake and clearance), binding potential (BP_{ND}) computed noninvasively using non-invasive Logan with cerebellar cortex as reference, and target region to cerebellum standardized uptake value ratio (SUVR) for both healthy volunteers (HVs) and AD subjects.

^{18}F-MK-6240 exhibited high initial brain uptake within about 3 min of tracer injection with SUV values of 3.5-6.0 followed by fast washout in low binding regions (80-85% at ~60 min post-injection) and moderate in high binding regions (30-50% decrease at ~60 min post injection), and by a slow and steady washout in all regions during ~60-180 min interval. Low concentration was found in the cerebellum and white matter.

In AD subjects, ^{18}F-MK-6240 showed elevated retention and SUVR values in regions expected to demonstrate tau pathology, with values of up to 4.0, compared to ~0.5-1.5 for the HV subjects. The pattern of uptake varied between AD patients and between hemispheres, consistent with known heterogeneity of tau pathology in AD. ^{18}F-MK-6240 metabolism was rapid with 7 ± 3% (n=5) intact parent remaining at 60 min post injection.

The results of this proof-of-concept human study suggest that ^{18}F-MK-6240 can detect tau pathology in AD and has suitable pharmacokinetic properties for quantitative measurements of tau pathology burden.

Three controls (age 68, 66, and 59 years) and one patient with AD (age 67 years, Mini Mental State Exam score 11) underwent PET imaging with ^{18}F-MK-6240 with arterial sampling for full quantification of the PET data. Images were acquired 0-90 min post-injection. Total V_T was calculated using the two-tissue compartment model with the metabolite-corrected arterial input function. V_T values were similar (~3.5 – 4.5 mL · cm^{-3}) across brain regions in the control subjects, with stable values after 60 min of scan time. In the AD patient, V_T values were elevated (6 – 9 mL · cm^{-3}) in amygdala, parahippocampal gyrus, and medial temporal cortex regions.

The cerebellum was used as reference region to calculate relative cortical binding with both kinetic modeling (Two tissue compartment model; distribution volume ration (DVR)) and simplified measurement (SUVR) using 60-90 min scan data. DVR and SUVR values showed strong correlation ($R^2 = 0.96$, $P < 0.0001$), suggesting SUVR can be used to quantify neurofibrillary tangle binding.
Florbetaben was evaluated in three single arm clinical studies (Study A-C) that examined images from adults with a range of cognitive function, including some end-of-life patients who had agreed to participate in a post-mortem brain donation program. Subjects underwent Florbetaben injection and scan, then had images interpreted by independent readers masked to all clinical

information. The Standard of Truth (SoT) was based on the histopathologic examination using Bielschowsky silver staining (BSS) of six brain regions assessed by a Pathology Consensus Panel masked to all clinical information (including PET scan results). Florbetaben PET imaging results (negative or positive) corresponded to a histopathology derived plaque score based on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria using neuritic plaque counts (Table 1). For the subject level SoT, if in any of the six regions β-amyloid neuritic plaques were more than sparse, the subject was classified as positive; if in none of the regions the β-amyloid neuritic plaques were assessed as being more than sparse, the subject was classified as negative.

Table 1: β-Amyloid Neuritic Plaque Counts Correlation to Image Results

Plaque Counts	CERAD Score	Neuraceq PET Image Result
<1	None	Negative
1 – 5	Sparse	
6 – 19	Moderate	Positive
≥20	Frequent	

Study A evaluated Florbetaben PET images from 205 subjects and compared the results to postmortem truth standard assessments of brain β-amyloid neuritic plaque density in subjects who died during the study. The median age was 79 years (range 48 to 98 years) and 52% of the subjects were male. By medical history 137 study participants had AD, 31 had other non-AD dementia, 5 had dementia with Lewy Bodies (DLB), and 32 had no clinical evidence of dementia. Interpretation of images from 82 autopsied subjects was compared to the subject level histopathology SoT. Three readers, after undergoing in-person tutoring, interpreted images using a clinically applicable image interpretation methodology (See Attachment C). At autopsy, the subject level brain β-amyloid neuritic plaque density category was: frequent (n = 31); moderate (n = 21); sparse (n = 17); or none (n = 13). Results from Study A are presented in Table 2 and Table 3.

Table 2: Neuraceq Results by Reader Training Method using BSS as Standard of Truth

Read Result		In-Person Training (Study A)	Electronic Media Training (Study B)
		n= 82	n=82
Sensitivity (%)	Median	98	96
	Range among the readers	96-98	90 -100
Specificity (%)	Median	80	77
	Range among the readers	77-83	47-80

Table 3: Neuraceq Correct and Erroneous Read Results by Reader Training Method

Read Result	In-Person Training (Study A)			Electronic Media Training (Study B)				
	Reader			Reader				
	1	2	3	4	5	6	7	8
Correct	75	74	75	73	65	71	73	69
False Negative	2	1	1	3	1	5	2	0
False Positive	5	7	6	6	16	6	7	13

BSS was the Histopathology Standard of Truth

In Study B five independent, blinded readers underwent the Electronic Media Training in the clinically applicable image interpretation methodology (See Attachment C) and assessed images from the same 82 end-of-life subjects who enrolled in Study A. The time interval between the Florbetaben scan and death was less than one year for 45 patients, between one and two years for 23 patients and more than two years for 14 patients. Results from Study B can also be found in Table 2 and Table 3.

Study C evaluated the reliability and reproducibility of the clinically applicable image interpretation methodology (see Attachment C) using the Electronic Media Training; 461 images from previous clinical studies were included from subjects with a range of diagnoses. Five new readers assessed randomly provided images from subjects with a truth standard (54 subjects who underwent an autopsy) and without a truth standard (51 subjects with mild cognitive impairment, 182 subjects with AD, 35 subjects with other dementias, 5 subjects with Parkinson's Disease and 188 HV). Among the 461 subjects, the median age was 72 years (range 22 to 98), 197 were females, and 359 were Caucasian. Image reproducibility data for various subject groups in Study C are presented in Table 4. Interreader agreement across all 5 readers had a kappa coefficient of 0.79 (95% CI 0.77, 0.83). The performance characteristics in 54 subjects with SoT were similar to those measured in Studies A and B. Additionally, intra-reader reproducibility was assessed from 46 images (10%); the percentage of intra- reader agreement for the 5 readers ranged from 91% to 98%.

Table 4: Reproducibility of Scan Results among Readers in Various Subject Groups[a]

Subject Group by Cognitive Status and Standard of Truth (SoT)	Positive Scans n[b]	Kappa (95% CI)	Percent of Scans with Inter-reader Agreement		
			3 of 5 readers agreed	4 of 5 readers agreed	5 of 5 readers agreed
All subjects (n=454)	212	0.80 (0.77, 0.83)	6	15	78
Subjects without SoT (n=394)	175	0.80 (0.77, 0.83)	6	15	79
Subjects with SoT (n=60)	37	0.75 (0.67, 0.83)	10	15	75
AD (n=176)	139	0.77 (0.72, 0.81)	7	10	83
HV (n=188)	26	0.55 (0.49, 0.58)	7	15	77
MCI (n=50, all without SoT)	28	0.84 (0.75, 0.92)	0	20	80
Other Dementias (n=40)	18	0.65 (0.55, 0.74)	8	33	60

[a]Subjects with missing scan interpretation (2 to 6% per group) were excluded from the analyses.
[b]Shown is the median number of scans interpreted as positive across the 5 readers for each group of subjects listed in the first column.
Alzheimer's disease (AD), Mild cognitive impairment (MCI), healthy volunteer (HV). Other dementias include DLB, fronto-temporal lobe dementia, vascular dementia, and dementia associated with PD.

1.5 Dose Rationale and Risk/Benefits

Single IV doses of [^{18}F]MK-6240 (up to ~185 MBq [5 mCi], containing ≤ 20 µg MK-6240) were generally well tolerated in healthy male and female subjects. In patients administered with the former Captisol formulation, (PN-001), 6 subjects (46.2%) reported a total of 3 treatment emergent AEs, of which one was considered by the primary investigator to be related to the study drug (frontal headache), (Table 5), which resolved spontaneously, and two were considered not related to study drug, rather method of administration (vascular access site bruising and vascular access site hematoma).

In the MNI-946 #e0061 study, using the current formulation, a sterile solution of up to 10% (v/v) ethanol, and 0.5% sodium ascorbate in saline (0.9% sodium chloride), one subject reported left wrist hematoma which was not considered related to study drug. There was no commonly recurring AE reported following [^{18}F]MK-6240 injection. All AEs were mild in intensity.

In the CE-01-JPN-18-01 study, also using the current formulation, two subjects reported adverse events prior to study drug administration. There were no adverse events reported post [^{18}F]MK-6240 dose.

Data from the meta-analysis of safety report (May 2020) and the two completed studies indicate that of 4,230 subjects exposed to [^{18}F]MK-6240 in ongoing trials at the time of the report, only 0.95% (39 subjects) experienced an AE and only 0.40% (17 subjects) experienced an AE that was considered related to injection of [^{18}F]MK-6240. One subject experienced two related AEs (headache and arthragia). There were no SAEs reported that were considered related to injection of [^{18}F]MK-6240. One unrelated SAE of pneumonia is recorded in the safety database. Other unrelated AEs reported in the meta-safety analysis study population included claustrophobia, anxiety, back pain, chest pain, musculoskeletal pain, nausea, hypertension, decreased blood glucose, skin irritation, falling and discomfort in the PET scanner.

Combined adverse event data from the above and ongoing studies evaluated with the data cutoff of 08 May 2022 are presented below. The most commonly occurring AEs that were related to injection of [^{18}F]MK-6240 included headache (ten subjects) and dizziness (three subjects). All 23 of the AEs reported in 22 subjects are listed in Table 5 and were considered possibly related to injection of [^{18}F]MK-6240.

No Suspected Unexpected Serious Adverse Reactions (SUSARs) have been reported (9825 patients total in completed (n=25) and clinical trials contributing to the global safety database (n=9800)).

There were no commonly recurring AEs reported following treatment with [^{18}F]MK-6240. All AEs deemed at least possibly related to [^{18}F]MK-6240 were mild in intensity.

No clinically significant abnormalities were noted in physical examinations, laboratory safety tests (chemistry, hematology, and urinalysis), VS, and ECGs. A meta-analysis of the safety database indicated that a majority of the studies contributing BP data demonstrated modest decreases in mean systolic and diastolic BP at the Post-injection Pre-scan time point while a majority of the studies demonstrated increases in mean systolic and diastolic BP at the Post-injection Post-scan time point. It is difficult to determine whether these BP changes are related to injection with [^{18}F]MK-6240 or whether they are related to the imaging procedures or other factors. BP monitoring before administration of an imaging agent and after imaging is routine in clinical practice and should continue a best practice for individuals [^{18}F]MK-6240. Furthermore, consistent with microdose patient exposures, injection with [^{18}F]MK-6240 does not appear to alter ECG recordings in any clinically significant manner.

There were no ECI, deaths or discontinuations due to an AE.

Table 5: Subjects With Adverse Events Considered Related to Study Drug By The Investigator (Incidence > 0% in One or More Treatment Groups)

	Completed Studies (n=25) MNI-946 #e0061 (n=6) PN-001 (n=13) CE-01-JPN-18-01 (n=6)		All studies contributing to the global safety database (n=9825)[a]	
	n	**(%)**	**n**	**(%)**
Subjects with one or more related adverse events	1	(4.0)	22	(0.22)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(0.01)**
Abdominal distension	0	(0.0)	1	(0.01)
General disorders and administrative site conditions	**0**	**(0.0)**	**2**	**(0.02)**
Injection Site Bruising	0	(0.0)	1	(0.01)
Injection Site Pruritis	0	(0.0)	1	(0.01)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(0.01)**
Arthralgia	0	(0.0)	1[b]	(0.01)
Nervous system disorders	**1**	**(4.0)**	**17**	**(0.17)**
Dizziness	0	(0.0)	4	(0.04)
Dysgeusia	0	(0.0)	1	(0.01)
Headache	1	(4.0)	10	(0.10)
Parosmia	0	(0.0)	1	(0.01)
Parosmia	0	(0.0)	1	**(0.01)**
Psychiatric disorders	**0**	**(0.0)**	**1**	**(0.01)**
Insomnia	0	(0.0)	1	**(0.01)**
Renal and Urinary Disorders	**0**	**(0.0)**	**1**	**(0.01)**
Dysuria	0	(0.0)	1	(0.01)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meet s the incidence criterion in the report title, after rounding.

[a] As of the cutoff date 08 May 2022, 9825 subjects had been exposed to [^{18}F]MK-6240 in completed and ongoing trials. This data includes expedited reports, if any in ongoing studies.

[b] This subject also reported headache and was the only subject in the safety database to report two related adverse events.

Three (3) healthy volunteers were included in the dosimetry study (two females and one male). For each subject, 10 whole body images over approximately 5 hours (^{18}F radionuclide, physical half-life is 109.77 min) were serially acquired according to standard procedures on a Siemens Biograph PET-CT camera. Three-dimensional volumes of interest were drawn to estimate total undecay corrected radioactivity exposures as a function of time in each organ of interest that takes up the tracer in significant and visually assessable amounts in addition to others that were delineated in the registered CT image (e.g. lungs and muscle). From these radioactivity exposure curves, the mean residence time of the radiotracer were calculated for each organ/tissue. These

values were entered into a human biodistribution model (Olinda/EXM) to calculate the effective dose (ED).

Evaluation of radiation dosimetry has been performed following administration of [^{18}F]MK-6240 in three healthy humans (two females and one male). The average (± SD) value of ED was 29.4 ± 0.6 µSv/MBq, which is in the typical range for ^{18}F-radiolabelled ligands. The radioactivity widely distributed to various body organs with organ absorbed doses largest for the gallbladder (202 µGy/MBq), small intestine (116 µGy/MBq), upper large intestine (128 µGy/MBq) and urinary bladder (128 µGy/MBq). Based on this, the administration of one 185 MBq (5 mCi) of [^{18}F]MK-6240 for PET scanning is anticipated to result in a total human ED of about 5.4 mSv.

The overall safety profile of Florbetaben is based on data from 978 administrations of Florbetaben to 872 subjects and 12 subjects who received vehicle only. No serious adverse reactions related to Florbetaben administration have been reported. The most frequently observed adverse drug reactions in subjects receiving Florbetaben were injection site reactions consisting of erythema, irritation and pain. All adverse reactions were mild to moderate in severity and of short duration.

The effective dose resulting from a 300 MBq (8.1 mCi) administration of Florbetaben in adult subjects is 5.8 mSv. The use of a CT scan to calculate attenuation correction for reconstruction of Florbetaben images (as done in PET/CT imaging) will add radiation exposure. Diagnostic head CT scans using helical scanners administer an average of 2.2 ± 1.3 mSv effective dose (CRCPD Publication E-07-2, 2007). A low-dose head CT attenuation scan administers a 0.04 mSv effective dose. The actual radiation dose is operator and scanner dependent.

Thus, the total combined radiation exposure from MK-6240 and Florbetaben administration and subsequent scan on a PET/CT scanner is estimated to be 5.4mSv + 5.8mSv + 2 * 0.04mSv = 11.28 mSv.

2 Study Objectives

The study employs tau PET imaging in a well-characterized multi-racial/ethnic cohort to examine the extent to which tau pathology is associated with cognition, differences in tau pathology across racial/ethnic groups, and the relationship between MRI markers of small-vessel cerebrovascular disease and tau pathology. The study also investigates amyloid-dependent tau spreading.

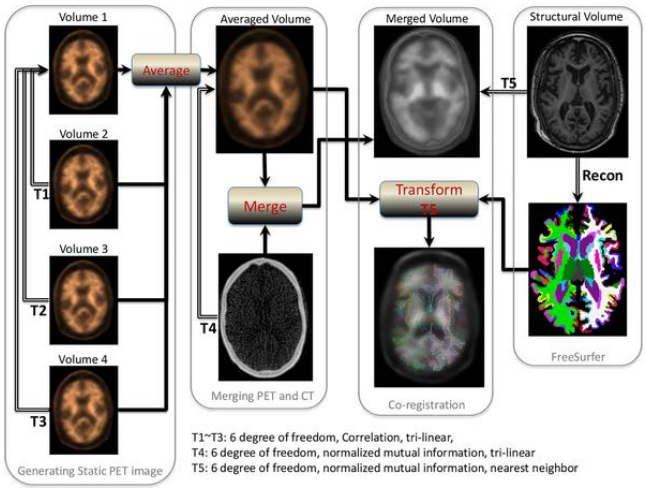
Regional SUVR for ^{18}F-MK-6240 will be calculated to investigate associations with measures of memory, olfactory function, and cerebrovascular disease, and amyloid positivity for ^{18}F-Florbetaben will be calculated to investigate the potential moderation of amyloid on the associations with tau.

3 Study Design

3.1 General Design

Tau and Aβ PET scanning takes place at the Kreitchman PET Center in the Radiology Department at Columbia University on separate days within 24 months of each other. ^{18}F-MK-6240 will be provided by Cerveau and ^{18}F-Florbetaben is provided by Life Molecular Imaging. Participant preparation includes intravenous catheterization followed by administration of 8.1 mCi as a slow single intravenous bolus (6 sec/mL) in a total volume of up to 10 mL of ^{18}F-Florbetaben for Aβ PET imaging and 5 mCi of ^{18}F-MK-6240 for tau PET. The ^{18}F- Florbetaben PET scans are acquired over a period of 20 minutes in 4 × 5 minute frames on an MCT PET/CT scanner (Siemens) in dynamic, 3D imaging mode beginning 90 minutes after injection. The ^{18}F-MK-6240 PET scans are acquired over a period of 30 to 60 minutes in 6 x 5 to 12 x 5 minute frames on the same scanner, beginning 60 to 80 minutes after injection.

Figure 6. Procedures for PET quantification



Transmission scans are done prior to the emission scan. An accompanying structural CT scan (in-plane resolution=0.58×0.58 mm, slice thickness=3mm, FOV=29.6×29.6 cm, number of slices=75) is also acquired. For quantitative analysis of tau and Aβ PET scans[20], dynamic PET frames are aligned to the first frame with rigid-body registration and a static PET image is obtained by averaging the four frames. The static PET image is then registered to the CT to obtain the inverse transformation matrix that transfers the CT image to the static PET image space. Each individual's MPRAGE MRI is also registered to the participant's CT image using normalized mutual information and tri-linear interpolation. Sets of regions-of-interest (ROIs) are selected from the FreeSurfer (FS)-segmented MRI scans. A combination of the two transformation matrices is used to transfer the ROI masks and the cerebellar grey matter from MRI space to static PET image space using nearest neighbor interpolation. These regional masks are used to extract the regional PET data. The SUV, defined as the decay-corrected brain radioactivity concentration normalized for injected dose and body weight, is calculated in selected regions. The SUV is then normalized to cerebellum grey matter to derive the SUVR. This process is illustrated in Figure 6.

For tau PET, in asymptomatic individuals tau pathology is typically restricted primarily to the medial temporal lobes [21-24] (corresponding to Braak Stage I/II) and tau pathology in this region appears to be selectively related to episodic memory [23, 24], so we will use bilaterial medial and inferior temporal cortex for the primary analysis of tau imaging. We will also quantitate SUVR in regions corresponding to Braak stage III/IV (limbic cortex), and stage V/VI (isocortex) [23] for secondary analyses. Tau SUVR data in all FreeSurfer-defined cortical regions will be databased for exploratory analyses.

For Aβ PET, SUVR values are derived in lateral temporal cortex, parietal cortex, and posterior

cingulate/precuneus as the primary ROIs. Using K-means clustering of log-transformed SUVR values, we derive cut scores for positivity following established procedures[25]. The overall rating is Aβ+ if any of the regions is considered positive. For the current study we are primarily concerned with whether participants are Aβ+, but we will also database continuous amyloid SUVR values in all FS-defined ROIs.

3.2 Primary Study Endpoints

The primary outcome measure with be regional SUVR values for ^{18}F-MK-6240 and Aβ+ for ^{18}F-Florbetaben.

3.3 Primary Safety Endpoints

The PET/CT imaging in this study is being undertaken for research purposes only and will not be reviewed clinically unless specifically requested. The majority of participants will receive or have received an MRI scan under a different protocol, which is reviewed clinically. A small number of participants are not eligible to receive an MRI scan due to contraindications, and therefore will not have had a clinical review.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

We will limit our recruitment into this study to people who are between 35 and 85 years old at the time of enrollment, with or without confirmed WHICAP parent history of AD, and who are currently enrolled in the ongoing Offspring Study. Recruitment will focus on those individuals who did or will undergo structural MRI scanning as part of this Offspring study within 18 months of PET study participation. A small number of subjects who enroll in the PET study may have contraindications to MRI scanning, for which we have an adjusted method of image analysis in place as described in Section 4.3 below.

The participants must meet the following:

1. Age 35-85 years
2. Have either mild cognitive impairment or mild clinical Alzheimer's disease; or have no problem with memory or thinking
3. Able to participate in all scheduled evaluations and to complete all required tests and procedures
4. Must be considered likely to comply with the study protocol and to have a high probability of completing the study

4.2 Exclusion Criteria

Exclusion criteria include pregnant or lactating women, conditions precluding entry into the scanners (e.g. claustrophobia, etc.), and inability to have a venous catheter for the injection of the radioligand.

Participants will be excluded from the study if any of the following applies:

1. Past or present history of certain brain disease other than mild cognitive impairment or mild clinical Alzheimer's disease
2. Certain significant medical conditions. Examples are uncontrolled epilepsy or multiple serious injuries
3. Unable to lie still for the duration of the PET scans
4. Radiation exposure for research studies in the last year that would put the subject past allowable limits if included in this study
5. Participation in the last year in a clinical trial for a disease modifying drug for AD unless it can be determined that the subject received a placebo and not an active drug
6. Conditions that preclude entry into the scanner (e.g., claustrophobia, etc.).
7. Inability to have a catheter placed in the vein for the injection of the dye
8. Currently pregnant or breastfeeding

4.3 Subject Recruitment and Screening

Adult children from the WHICAP study are currently being recruited into the Offspring Study. The parents are a selected subset of participants in WHICAP who are active (seen at the most recent assessment wave) or inactive (deceased, moved, too ill to participate) and seen at baseline and at least one follow-up. We recruit from families in which parents with and without AD are demographically matched. Table 6 shows the number of WHICAP families from which we are recruiting offspring, given the current prevalence of AD among WHICAP participants and the expected conversion rate over 5 years among active participants. Our preliminary data suggest that on average, we will have access to two to three offspring who live in the greater NYC area.

We plan to assess 600 offspring per year for all five years of the Offspring Study, and obtain medical, neuropsychological, and functional data from an in-person visit. We are recruiting approximately 33% of the offspring to participate in brain MRI. These 1,000 (n=200 per year) offspring will be representative of the cohort at large with respect to parent diagnosis, race/ethnicity, and sex. All offspring will be screened for eligibility for structural brain MRI. Table 6 shows our expected MRI recruitment based on our experience in the WHICAP study, our pilot interview data of offspring, and conservative estimates of eligibility and willingness to be scanned. Only one offspring per family will be recruited for the MRI. If there are more than one offspring who are eligible for MRI within a family, we select the oldest. Of eligible families, we expect that 75% of offspring will be eligible after screening for MRI contraindications, and of those, 60% will be willing to participate (willingness rate was 79% in our survey), and thus we will have 1,079 eligible and willing MRI participants.

TABLE 6. Recruitment

	White		Black		Hispanic	
	no AD	AD	no AD	AD	no AD	AD
Active WHICAP parents	547	100	494	206	903	505
Inactive WHICAP parents	460	59	452	109	421	162
Parents with children (75%)	755	119	710	236	993	500
Assent/locate (95%/50%)	562	93	521	188	801	421
Other parent AD-free (90%)	506	n/a	469	n/a	721	n/a
# offspring avail (2 per fam)	1012	187	939	375	1442	841
MRI elig. (1 per fam; 75%)	380	70	352	141	541	315
MRI willing (60%)	228	42	211	84	325	189

Aβ and tau PET scans will be obtained on a representative subset of 150 offspring (with and without positive family history of AD) between the age of 35 and 85. We will prioritize individuals who have already undergone or will undergo structural MRI as part of the Offspring Study. We will obtain both PET scans within 24 months of each other. Therefore, about 33 individuals per year will be recruited and scanned for contemporaneous Aβ and tau PET and MRI scanning. MRI scans will be completed up to 18 months prior to the first PET scan, or up to 18 months after the last PET scan. Since MRI scanning has already commenced in the overall study, we will re-acquire MRI scans (with other funds) in instances when the initial scan falls outside of the 18-month window. A subset of PET eligible subjects may be ineligible for MRI scans due to contraindications. To allow us to continuously meet recruitment goals, we will still obtain PET scans on these individuals and use an adjusted statistical method during data analysis. Specially, PET data collected without MRI data will be quantified as parametric standard uptake value ratio (SUVR) images using atlas-based regions of interest (ROIs) rather than subject-specific, MRI-based ROIs. The Montreal Neurological Institute (MNI) brain atlas will undergo a non-linear spatial transform to PET space. An inferior cerebellar gray matter ROI from the MNI template will be used as reference region. Alzheimer's disease specific ROIs from the MNI template will be used to derive mean SUVRs. A covariate for analysis method (atlas-based ROIs vs subject-specific, MRI-based ROIs) will be included in all statistical analyses.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn if they experience any serious adverse reactions to the radioligand or during the participation in the study.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

No data collection will occur after withdrawal in subjects who drop out of the study. If data was collected prior to withdrawal, such data will be analyzed if possible.

5 Study Drug

5.1 Description

^{18}F-MK-6240 is a novel tau radioligand recently developed by Merck & Co., Inc [26]. ^{18}F-MK-6240 shows favorable binding properties in both human brain homogenates and rhesus monkey brain PET studies [27]. Pharmacological studies have shown that the unlabeled compound MK-6240 is not expected to have any significant binding to other targets that would confound measurement of tau aggregation. Early human PET studies have shown that ^{18}F-MK-6240 binding is elevated in AD patients, and that resulting radiation exposure is within the range of other ^{18}F radioligands.

Florbetaben is indicated for PET imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. A negative Florbetaben scan indicates sparse to no amyloid neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient’s cognitive impairment is

due to AD. A positive Florbetaben scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Florbetaben is an adjunct to other diagnostic evaluations.

5.2 Preparation and Administration of Study Drug

Participant preparation includes intravenous catheterization followed by administration of 8.1 mCi as a slow single intravenous bolus (6 sec/mL) in a total volume of up to 10 mL of ^{18}F-Florbetaben for Aβ PET imaging and 5 mCi of ^{18}F-MK-6240 for tau PET.

^{18}F-MK-6240 will be formulated in clear solution of up to 10% (v/v) ethanol, and 0.5% sodium ascorbate in saline (0.9% sodium chloride) for IV bolus administration.

^{18}F-Florbetaben is supplied in a 30 mL glass vial containing up to 30 mL of a clear solution at a strength of 50 to 5000 MBq/mL (1.4 to 135 mCi/mL) ^{18}F-florbetaben at end of synthesis. Each vial contains multiple doses and is enclosed in a shielded container to minimize external radiation exposure.

5.3 Packaging

N/A since ^{18}F-MK-6240 will be packaged and provided by Cerveau and ^{18}F-Florbetaben will be packaged and provided by Life Molecular Imaging.

5.4 Receiving, Storage, Dispensing and Return

5.4.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.4.2 Storage

Store ^{18}F-Florbetaben and ^{18}F-MK-6240 at room temperature 25°C (77°F); excursions permitted to 2°C to 42°C (36°F to 108°F). The product does not contain a preservative. Store within the original container or equivalent radiation shielding. Radiotracer must not be diluted.

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

5.4.3 Dispensing of Study Drug

Slow bolus (6 sec/mL) IV injection of 5 mCi ^{18}F-MK-6240 and 8.1 mCi ^{18}F-Florbetaben on the same day as delivery to the Columbia University Medical Center PET Department.

For ^{18}F-MK-6240, the carrier mass dose will be limited to no more than 20 μg per injection. For ^{18}F-Florbetaben, the carrier mass dose will be limited to no more than 30 μg per injection.

5.4.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Tau PET

The ^{18}F-MK-6240 PET scans are acquired over a period between 30 to 60 minutes in 6 to 12 x 5 minute frames on the same scanner, beginning 60 to 80 minutes after injection.

Transmission scans are done prior to the emission scan. An accompanying structural CT scan (in-plane resolution=0.58×0.58 mm, slice thickness=3mm, FOV=29.6×29.6 cm, number of slice=75) is also acquired.

6.2 Amyloid PET

The ^{18}F-Florbetaben PET scans are acquired over a period of 20 minutes in 4 × 5 minute frames on an MCT PET/CT scanner (Siemens) in dynamic, 3D imaging mode beginning 90 minutes after injection.

Transmission scans are done prior to the emission scan. An accompanying structural CT scan (in-plane resolution=0.58×0.58 mm, slice thickness=3mm, FOV=29.6×29.6 cm, number of slice=75) is also acquired.

The second PET visit will occur within 24 months of the first. There is no particular order that the participants must receive the study drugs. If eligible, the MRI scan will be collected up to 18 months prior to the first PET visit, or up to 18 months after the second PET visit.

6.3 Questionnaires

Participants may be asked to complete any number of outstanding questionnaires during the PET scan uptake periods. The questionnaires are self-administered and are part of the planned data collection for the main Offspring study.

7 Statistical Plan

7.1 Sample Size Determination

The sample size of 150 subjects was selected to allow sufficient power ($\geq$ 80%) of a two-sided significance test with α = 0.05 to detect meaningful effects associated with the primary hypotheses. We used the G*Power[28] to perform the following power analyses.

7.2 Statistical Methods

Regional SUVR for ^{18}F-MK-6240 will be calculated to investigate associations with measures of memory, olfactory function, and cerebrovascular disease, and amyloid positivity for ^{18}F-Florbetaben will be calculated to investigate the potential moderation of amyloid on the associations with tau.

Before any specific statistical modelling techniques are applied, we will examine all variables for illegitimate values, outliers, and other inconsistencies. Distributions of demographic and other clinically important variables will be examined and summarized by means, standard deviations, minima, and maxima for continuous measures and proportions for categorical measures. Similar descriptive analyses will be conducted on all outcome variables of interest. We will make every effort to obtain all data to reduce or eliminate missing data issues. Tests will be two-sided and performed at a significance level of α=0.05. After descriptive examination of the variables of interest, a series of unadjusted or partially adjusted planned analyses will be conducted to address the specific hypotheses, followed by fully adjusted models, follow-up analyses, and exploratory analyses. In all regression analyses, steps will be taken to avoid issues related to multicollinearity of the predictors. If necessary, data reduction techniques (e.g., screening out variables that are highly correlated) will be applied to the predictors prior to fitting the regression models.

7.3 Subject Population(s) for Analysis

The study builds on an over-25-year history of studying cognitive aging and dementia in the community through the WHICAP study and the newly-established Offspring Study, in which 3,000 adult children of participants in the WHICAP study are being recruited and evaluated comprehensively, and 150 Offspring participants will undergo PET imaging. This racially/ethnically diverse subject population will allow the examination of sources of health disparities and the examination of biomarkers in established community-based diverse cohorts, utilizing existing cohorts. We have detailed characterization of both the parental and offspring generations, including consensus diagnosis based on detailed in-person assessment, longitudinal cognitive data, risk factors, and date of onset. Unlike many other offspring cohorts, our Offspring Study has direct assessment of parental AD status among a community-based sample. Finally, we will be at the leading edge of examining the interplay of cerebrovascular disease and AD pathology, both of which occur at higher prevalence in racial/ethnic minorities, by being among the first to examine the relationship between markers of cerebrovascular disease and tau pathology *in vivo*.

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