2 SYNOPSIS

SPONSOR:	**Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	MK-6240	
INDICATION:	Alzheimer's Disease	
PROTOCOL TITLE:	A Study to Qualify [^{18}F]MK-6240 Positron Emission Tomography (PET) for Use as a Biomarker of Neurofibrillary Tangle Pathology in Alzheimer's Disease	
TRIAL IDENTIFIERS:	Protocol Number:	P001
	Clinical Phase:	1
	EudraCT Number:	2015-001659-58
ETHICS:	This trial was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.	
TRIAL CENTERS:	This trial was conducted at a single center.	

DESIGN:	This was an open-label, 2-part study including both healthy subjects and patients with Alzheimer's disease (AD) or amnestic mild-cognitive impairment (MCI). Part 1 was the first administration of [^{18}F]MK-6240 in humans. Part 1 evaluated the safety and tolerability of [^{18}F]MK-6240, as well as, the radiation safety profile and biodistribution (dosimetry) of [^{18}F]MK-6240 in healthy young subjects (18 to 55 years of age [yoa]). Subjects received a single IV dose of [^{18}F]MK-6240 (~180 MBq), followed by a series of whole body (WB) PET scans, clinical examinations, and laboratory safety evaluations. Part 2 was designed to: 1) to determine optimal imaging protocol parameters for [^{18}F]MK-6240 quantification of regional neurofibrillary tangle (NFT) load; 2) to ascertain the specificity of the signal through qualitative comparison of images from patients with AD (across a range of disease stages), patients with amnestic MCI (56 to 85 yoa), and healthy elderly (HE) subjects (56 to 85 yoa); 3) to explore potential of [^{18}F]MK-6240 to discriminate between disease severity as registered by the Mini-Mental State Examination (MMSE) status scores, using standardized imaging protocols not requiring an arterial input function, and finally; and 4) to determine test retest (T-RT) characteristics of the PET signal in AD/MCI patients. Because this was a Phase 1 assessment of [^{18}F]MK-6240 in humans, the tracer kinetic and safety profiles of the compound were still being elucidated. This protocol was written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical trials.	
	Planned duration of Part 1:	6 weeks
	Planned duration of Part 2:	1 year

Objectives	Primary Part 1: 1. Objective: To evaluate the safety and tolerability of a single IV dose of [^{18}F]MK-6240 in healthy subjects. 2. Objective: To evaluate the WB and internal organ radiation absorbed doses following a single IV dose of [^{18}F]MK-6240 in healthy subjects. Part 2: 1. To investigate the safety and tolerability of single IV doses (up to 2 injections) of [^{18}F]MK-6240 in patients with AD amnestic MCI, and in cognitively normal elderly adults. 2. To determine optimal parameters for [^{18}F]MK-6240 quantification of tracer binding in AD brain with PET by providing preliminary characterization of (1) estimates of regional cerebral kinetics; and (2) ability to provide estimates of study subjects' regional volume of distribution (V_T) and surrogates of V_T (ie, standardized uptake value ratio [SUVR]). 3. To evaluate [^{18}F]MK-6240 tracer binding in a cross section of elderly subjects with a spectrum of AD (including HE). 4. To evaluate intra-subject T-RT variability of the surrogate measurements of V_T (eg, SUVR) in brain regions of interest (ROIs) following IV administration of 2 single doses of [^{18}F]MK-6240 in a cross section of elderly subjects with a spectrum of AD.
Hypotheses	Primary Part 1: Dosimetry calculations based on Part 1 data will support ≥2 [^{18}F]MK-6240 injections in humans per annum. Part 2: The intra-subject T-RT variability of the surrogate measurements of V_T (eg, SUVR) in brain regions associated with NFT deposition in AD is ≤10%.

Treatment groups	Part 1	Single IV dose of [^{18}F]MK-6240, ~180 MBq (containing ≤20 µg MK-6240) 3 subjects (actual)	
	Part 2	Single IV dose of [^{18}F]MK-6240, ~160 MBq (containing ≤20 µg MK-6240) 10 subjects (actual); 2 patients received a repeat dose on a separate occasion for T-RT purposes.	
Endpoints and definitions	Part 1: Co-Primary endpoint	Safety and Tolerability in healthy subjects	
		Dosimetry in healthy subjects following a single IV dose of [^{18}F]MK-6240	Quantitative assessments of radiation exposure from [^{18}F]MK-6240 to the whole body and its internal organs, including the brain, was assessed as organ absorbed doses and effective dose (ED).
	Part 2: Co-Primary endpoint	Safety and Tolerability in patients with AD amnestic MCI and cognitively normal elderly adults	
		Preliminary characterization of [^{18}F]MK-6240 quantification of tracer binding in AD brain with PET	Brain regional [^{18}F]MK-6240 time activity curves (TACs) and arterial metabolite-corrected plasma input function were used to determine indices of tracer binding – SUVR and/or total V_T.
		[^{18}F]MK-6240 tracer binding in a cross section of elderly subjects with a spectrum of AD (including HE)	Brain regional [^{18}F]MK-6240 TACs and arterial metabolite-corrected plasma input function were used to determine indices of tracer binding – SUVR and/or total V_T.

		Intra-subject test-re-test variability of the surrogate measurements of V_T (eg, SUVR) in brain ROIs following IV administration of 2 single doses of [^{18}F]MK-6240 in a cross section of elderly subjects with a spectrum of AD	Approximately 10% or lower intrasubject T-RT variability in SUVR or V_T in NFT deposition regions would indicate that [^{18}F]MK-6240 measures the intended target with adequate precision.
Trial status	19-OCT-2015, first subject first visit to 27-DEC-2016, last subject last visit		
Database lock	18-APR-2017		
RESULTS AND ANALYSIS:	Three (3) subjects were enrolled in Part 1 of the study and 10 subjects (4 HE and 6 patients with MCI/AD) were enrolled in Part 2. No subjects discontinued from the study prematurely. Enrollment in the study was discontinued due to updates in the business and development stategy of the MK-6240 PET tracer program, as summarized in a communication with the investigator on 24-Jan-2017. Per protocol, the decision to halt conduct of the study for reasons other than safety did not meet the definition of a pause or an early study termination. Statistical analyses for Part 1 were conducted as outlined in the protocol. Due to the evolving development strategy for the MK-6240 PET tracer as the study was ongoing, recruitment into the the study was suspended before a sufficient number of informative retest scans could be obtained, and thus the intended characterization of retest variability (RV) was not possible.		

Subject Characteristics

	Part 1 Healthy Volunteers		Part 2 Healthy Elderly Volunteers		Part 2 MCI / AD† Patients		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	3		4		6		13	
Gender								
Male	1	(33.3)	3	(75.0)	5	(83.3)	9	(69.2)
Female	2	(66.7)	1	(25.0)	1	(16.7)	4	(30.8)
Age (Years)								
18 to 85	3	(100.0)	4	(100.0)	6	(100.0)	13	(100.0)
Mean	27.0		65.3		73.2		60.1	
SD	7.9		5.4		4.4		19.9	
Median	24.0		66.0		74.0		67.0	
Range	21 to 36		58 to 71		67 to 80		21 to 80	
Race								
White	3	(100.0)	4	(100.0)	6	(100.0)	13	(100.0)
Ethnicity								
Not Hispanic Or Latino	3	(100.0)	4	(100.0)	6	(100.0)	13	(100.0)

† MCI / AD = Mild Cognitive Impairment / Alzheimer's Disease

Disposition of Subjects

	Part 1		Part 2		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	3		10		13	
Trial Disposition						
Completed	3	(100.0)	10	(100.0)	13	(100.0)
Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.						

Analysis description	**Co-primary Analyses Part 1 and Part 2: Safety** Incidence of AEs were descriptively summarized.
Analysis population and time point description	*All Subjects as Treated* (AST) - All subjects who received at least 1 dose of the investigational drug were included in the assessments of safety and tolerability. Safety and tolerability were assessed throughout the study by monitoring subjects for clinical AEs.
Summary	There were no deaths, serious adverse events, or events of clinical interest reported in this study. Six (6) of the 13 subjects enrolled reported AEs. One (1) healthy subject reported a headache within 5 hours of a single IV dose of approximately 180 MBq (5 mCi) [^{18}F]MK-6240, containing ≤20 µg MK-6240. The headache was mild, resolved spontaneously, and was considered related to study drug by the investigator. Five (5) subjects in Part 2 reported AEs characterized as vascular access site bruising or site hematoma within 48 hours of dosing. All events were considered mild and unrelated to study drug by the investigator. All but 1 incident of hematoma resolved before discharge from the study. There were no clinically meaningful trends observed in ECG, VS, or laboratory safety assessments in this study.

Subjects With Adverse Events (Incidence >0% in One or More Treatment Groups)

	Part 1		Part 2		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	3		10		13	
with one or more adverse events	1	(33.3)	5	(50.0)	6	(46.2)
with no adverse events	2	(66.7)	5	(50.0)	7	(53.8)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**5**	**(50.0)**	**5**	**(38.5)**
Vascular access site bruising	0	(0.0)	2	(20.0)	2	(15.4)
Vascular access site haematoma	0	(0.0)	3	(30.0)	3	(23.1)
Nervous system disorders	**1**	**(33.3)**	**0**	**(0.0)**	**1**	**(7.7)**
Headache	1	(33.3)	0	(0.0)	1	(7.7)

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 meets the incidence criterion in the report title, after rounding.

Analysis description	Co-primary Analysis Part 1: Dosimetry in healthy subjects following a single IV dose of [^{18}F]MK-6240
Analysis population and time point description	Three (3) healthy subjects were included in the dosimetry study (2 females and 1 male, 27 ± 8 yoa). In each subject, 10 WB images over approximately 5 hours time (^{18}F radionuclide, physical half-life is 109.77 minutes) were serially acquired according to standard procedures on a Siemens Biograph PET-computed tomography (CT) camera after microdose (≤20 µg) administration of [^{18}F]MK-6240. Three-dimensional volumes of interest were drawn to estimate the percentage of injected activity in each organ of interest that takes up the tracer in significant and visually assessable amounts. The quantified data were subsequently converted into TACs and retention of radioactivity in these regions (residence times) were calculated for each organ/tissue. These values were entered into a human biodistribution model (Olinda/EXM) to calculate the whole body ED. The ED is a measure of stochastic risk associated with exposure to low levels of ionizing radiation and hence, only valid for administration of tracer amounts of the compound in humans.
Summary	The organ absorbed doses were largest for the gallbladder (202 µGy/MBq), small intestine (116 µGy/MBq), upper large intestine (128 µGy/MBq) and urinary bladder (128 µGy/MBq). The average (± standard deviation [SD]) value of effective dose (ED) was 29.4 ±0.6 µSv/MBq, which is in the typical range for ^{18}F radiolabelled ligands. Based on this, the administration of one 160 MBq (4.3 mCi) of [^{18}F]MK-6240 for PET scanning (including CT scanning) is anticipated to result in a total human ED of about 4.8 mSv that supports ≥2 injections per annum.

Radiation dosimetry estimates for [^{18}F]MK-6240 determined from 3 healthy subjects

	Radiation Dose
Organ	**µGy/MBq**
Adrenals	12.7 ± 1.0
Brain	8.8 ± 0.4
Breasts	5.8 ± 0.9
Gallbladder Wall	202.0 ± 111.0
LLI Wall	46.4 ± 5.5
Small Intestine	116.0 ± 13.3
Stomach Wall	16.9 ± 3.7
ULI Wall	128.0 ± 15.7
Heart Wall	15.6 ± 1.0
Kidneys	33.5 ± 4.8
Liver	34.3 ± 9.2
Lungs	19.7 ± 3.6
Muscle	9.4 ± 0.8
Ovaries	28.3 ± 2.0
Pancreas	14.6 ± 1.1
Red Marrow	19.2 ± 2.9
Osteogenic cells	16.9 ± 1.5
Skin	5.6 ± 0.8
Spleen	17.7 ± 3.9
Testes	3.0 ± 5.1
Thymus	6.9 ± 1.1
Thyroid	5.6 ± 1.5
Urinary Bladder Wall	128.0 ± 31.8
Uterus	26.4 ± 1.2
Total Body	12.2 ± 0.7
Effective dose (µSv/MBq)	**29.4 ± 0.6**

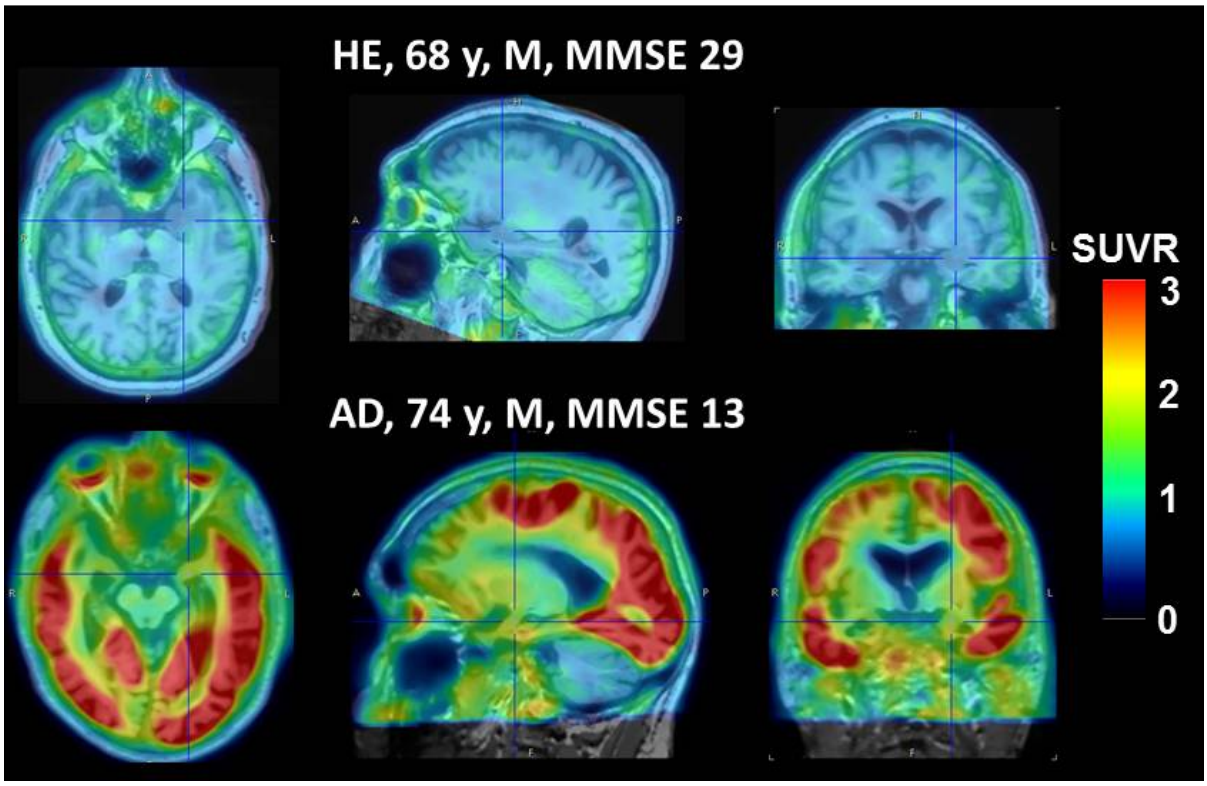
Values are mean ± SD.

Analysis description	Co-primary Analysis Part 2: Preliminary characterization of [^{18}F]MK-6240 quantification of tracer binding in AD brain with PET
Analysis population and time point description	Six (6) subjects with mild to moderate AD were enrolled in the study (5 males and 1 female, 73 ± 4 yoa). Each subject received a bolus IV injection (<185 MBq, ≤20 µg) of [^{18}F]MK-6240 followed by 1.5 to 2.5 hour dynamic brain PET scan. During the PET scan, arterial blood samples were collected in some subjects to measure blood/plasma total and parent radiotracer concentrations. [^{18}F]MK-6240 uptake in AD brain was high with a peak SUV (standardized uptake value) of approximately 5, followed by retention of radioactivity uptake across neuroanatomical regions characterized by NFT accumulation (Figure 1 and Figure 2). Quantification methods included simple ratio methods, reference tissue modeling approaches that uses reference region devoid of target NFTs, as well as kinetic modeling methods such as compartmental models in subjects where arterial input function was available. The SUV ratio (SUVR), calculated as a ratio between the activity in the target region divided by the activity in the cerebellum measured between 60-90 minute, were about 3-4 in brain regions known to be rich in NFTs (Figure 3A). The unconstrained two-tissue compartment model better fit the [^{18}F]MK-6240 time-activity curves (TACs) than one-tissue compartment model for all regions in AD subjects. Absolute quantification of brain uptake in terms of V_T across regions was 6-10 mL/cm^3 in temporal and medial temporal cortex of AD subjects indicating NFT associated binding in those regions. The V_T values were stable over time after approximately 60 minutes post injection indicating negligible influence of any radiometabolite contamination to brain signal (Figure 3B).
Summary	High SUVR in the order of 3-4 and V_T values in the order of 6-10 mL/cm^3 were observed in brain regions of AD expected to be rich in NFTs.

Analysis description	**Co-primary Analysis Part 2: [^{18}F]MK-6240 tracer binding in a cross section of elderly subjects with a spectrum of AD (including Healthy Elderly)**
Analysis population and time point description	Four (4) HE subjects were enrolled in the study (3 males and 1 female, 66 ± 5 y old). Each subject received a bolus IV injection (<185 MBq, ≤20 µg) of [^{18}F]MK-6240 followed by 2.5 hour dynamic brain PET scan. During the PET scan, arterial blood samples were collected in some subjects to measure blood/plasma total and parent radiotracer concentrations. [^{18}F]MK-6240 uptake in HE brain was homogenous, high with a peak SUV of approximately 5, followed by rapid washout of radioactivity across brain regions to a low uniform level (Figure 1 and Figure 2). The SUVR values were approximately 1 with V_T values uniformly low approximately 4 mL/cm^3 and stable across brain regions (Figure 3) consistent with low potential for non-specific (non-NFT) binding.
Summary	An SUVR of 1 with uniformly low V_T values across brain regions in HE suggest negligible to no off-target binding

Analysis description	**Co-primary Analysis Part 2: Intra-subject test-re-test variability of the surrogate measurements of V_T (eg, SUVR) in brain regions of interest (ROIs)**
Analysis population and time point description	The T-RT scans were obtained in only 2 of 6 AD subjects. Due to technical and logistical issues, the -T-RT scans in one subject were separated by 4 months. The average retest RV over several cortical regions for 1 subject (4 month scan difference) was <10%. In the other subject, significant motion in the retest scan was observed such that, variability could not be accurately assessed. Due to the evolving development strategy for the MK-6240 PET tracer as the study was ongoing, recruitment into the the study was suspended before a sufficient number of informative retest scans could be obtained, and thus the intended characterization of RV was not possible.
Summary	Measurement of RV is incomplete due to inadequate enrollment of subjects.

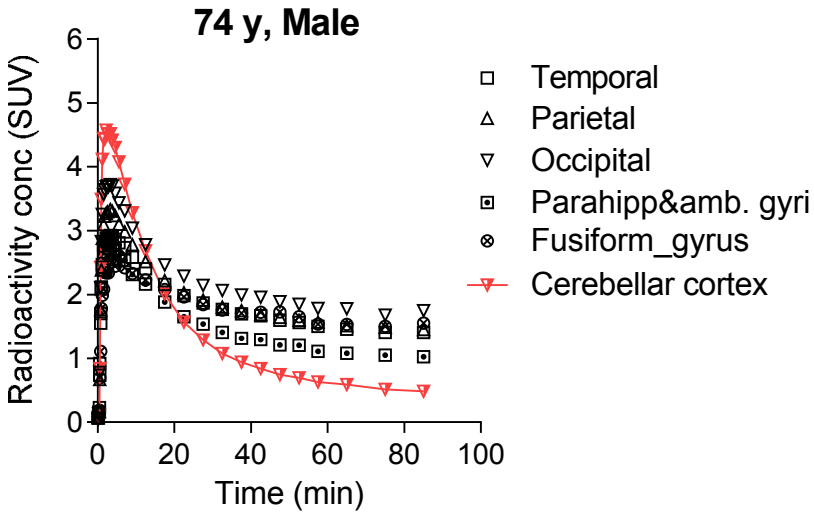
Figure 1 [18F]MK-6240 PET Images Fused to Individual MRI of a Healthy Elderly (HE) Subject (top) and a Patient with Alzheimer's Disease (AD; Bottom)



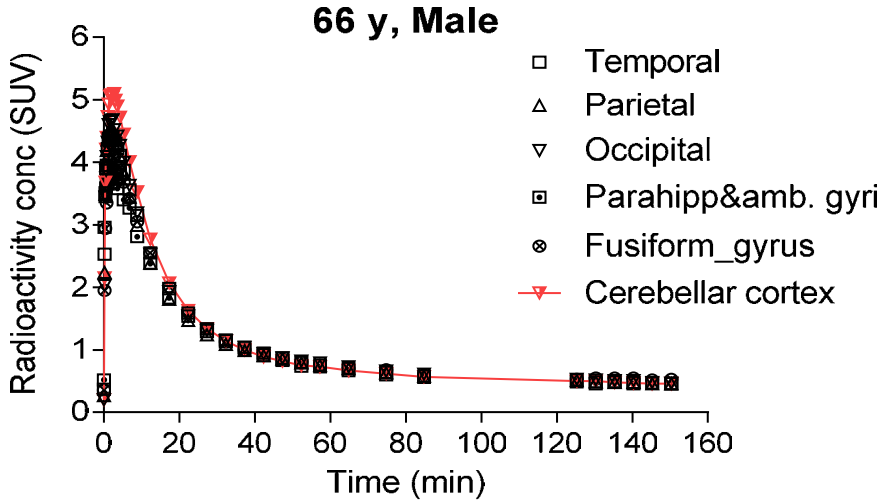
The PET Image is averaged between 60-90 min scan time and is scaled as standardized uptake value ratio (SUVR) with cerebellar cortex as reference region. MMSE – Folstein Mini-Mental State Examination score.

Figure 2 Regional Brain Radioactivity Concentration (standardized uptake value [SUV]) Time Course After Intravenous Injection of [18F]MK-6240

A



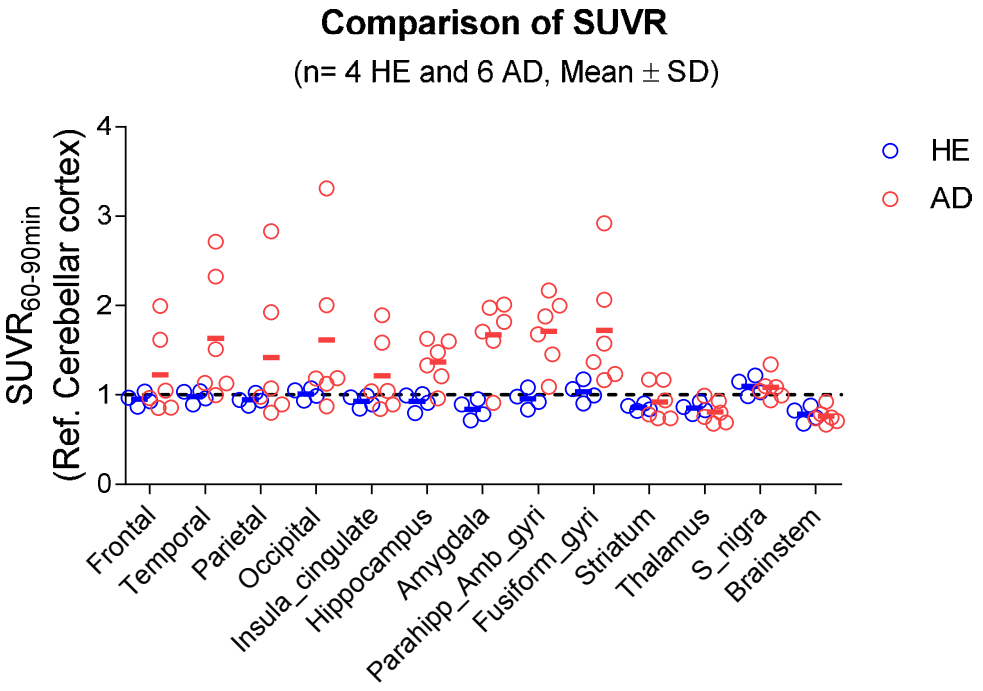
B



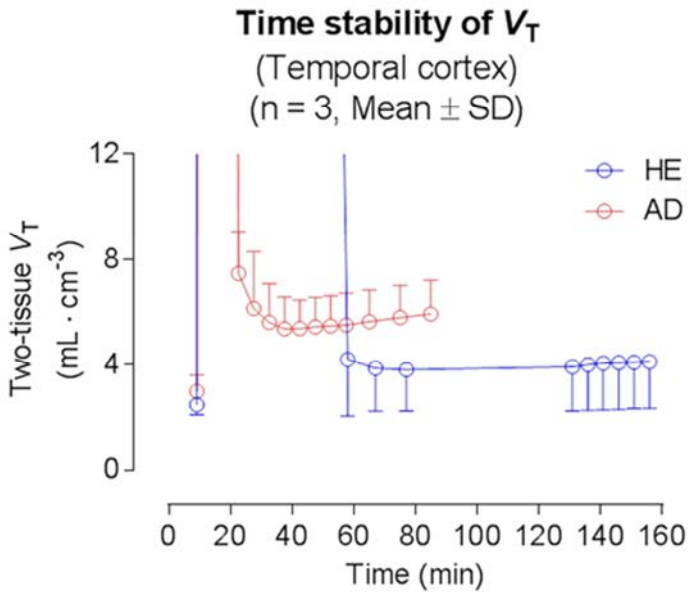
A representative patient of Alzheimer's Disease with Folstein Mini-Mental State Examination score (MMSE) score of 13 (A) and a healthy elderly subject with MMSE score of 29 (B).

Figure 3 Standardized Uptake Value Ratio (SUVR) Across Brain Regions of Healthy Elderly (HE) and Patients With Alzheimer's Disease (AD)

A



B



The SUVR values are average between 60-90 minute scan time with cerebellar cortex as reference region (A). Time stability of regional volume of distribution (V_T) values in temporal cortex across HE and AD populations (B).

CONCLUSIONS:	1. Single IV doses of [^{18}F]MK-6240 in healthy subjects, and up to 2 single IV doses administered in patients with AD/MCI and in cognitively HE subjects are well tolerated. 2. Dosimetry findings support the intended use of the [^{18}F]MK-6240 tracer. 3. Tracer uptake differences between cognitively normal HE and patients with AD/MCI are consistent with [^{18}F]MK-6240 specificity and sensitivity to NFT deposition in AD in vivo.
PUBLICATION(S):	1. Lohith T, Bennacef I, Zeng Z, Holahan M, Koole M, Van Laere K, Sur C, Struyk A, Walji A, Hostetler E. Preclinical evaluation and first-in-human dosimetry of [^{18}F]MK-6240, a new PET tracer for in vivo quantification of human neurofibrillary tangles. J Nucl Med 2016;57(S2):125. 2. Bennacef I, Zeng Z, Lohith T, Miller PJ, Salinas CA, Connolly BM, Gantert LT, et al. Discovery and First-in-Human Evaluation of the Tau-Imaging PET Radiotracer [^{18}F]MK-6240. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2016;12(7):501-502. 3. Lohith T, Bennacef I, Sur C, Declercq R, Serdons K, Bormans G, Hostetler E, Van Laere K, Vandenberghe R, Struyk A. Quantification of [^{18}F]MK-6240, a new PET tracer targeting human neurofibrillary tangles (NFTs) in brain of healthy elderly and subjects with Alzheimer's disease. J Nucl Med 2017;58(S1):277.
REPORT DATE:	29-AUG-2017