2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)

COMPOUND NAME: MK-6884

PROTOCOL TITLE: A Three-Part Trial to Qualify [^{11}C]MK-6884 Positron Emission Tomography for Use as a Biomarker for Regional M4 PAM Receptor Density Quantification in the Human Brain

STUDY IDENTIFIERS:

IND: 127,788	EudraCT: 2015-001631-20	WHO: N/A	NCT: NCT02621606
Other: N/A			

STUDY PHASE: 1

INDICATION: Alzheimer's disease (AD)

STUDY CENTERS: This study was conducted at 2 centers in 2 countries.

STUDY STATUS: This study is complete; this report is based on the final analysis.

First Subject, First Visit	Last Subject, Last Visit	Database Lock Date
08-JAN-2016	28-DEC-2017	01-MAR-2018

METHODOLOGY: This was an open-label, 3-part study in healthy adult subjects (18 to 55 years inclusive; Part I), healthy elderly subjects (55 to 85 years, inclusive; Part II), and moderate to severely impaired patients with AD (55 to 85 years inclusive, Part III) to assess safety and pharmacodynamics (PD) following single doses of [^{11}C]MK-6884. In Part I, a single, previously defined intravenous (IV) dose of [^{11}C]MK-6884 ~ 133 to 360 MBq (~ 3.6 to 9.7 mCi, ≤4.9 μg) was administered to subjects followed by a series of whole-body positron emission tomography (PET) scans, clinical examinations and laboratory safety evaluations. In Part II, a baseline magnetic resonance imaging (MRI) scan of the brain was obtained for region-of-interest (ROI) delineation. Subjects were given 2 separate IV doses of [^{11}C]MK-6884 ~ 161 to 358 MBq (~ 4.3 to 9.7 mCi, ≤4.9 μg) with a brain PET/computed tomography scan performed after each dose. The PET images of the brain were obtained for up to approximately 90 minutes after each administration of [^{11}C]MK-6884. There was a wash-out of at least 3 hours between each [^{11}C]MK-6884 administration to allow for most of the radioactivity from the first scan to decay prior to starting the second scan. In Part III, a baseline MRI scan of the brain was obtained for ROI delineation and to ensure that the MRI scan was consistent with a diagnosis of moderate to severe AD. A single brain scan was performed after dosing with [^{11}C]MK-6884 ~ 325 to 479 MBq (~ 8.8 to 13.0 mCi, ≤4.9 μg), and PET images of the brain were obtained for approximately 90 minutes after the administration of [^{11}C]MK-6884 to enable determination of the non-displaceable binding potential (BP_{ND}) of the [^{11}C]MK-6884 ligand.

In all parts of the study, clinical and laboratory safety evaluations were performed up to ~ 3 hours following administration of each dose of [^{11}C]MK-6884.

Study Part	PET Tracer	Target Dose/Potency	Dose Frequency	Route of Administration
Part I	[^{11}C]MK-6884	~ 370 MBq (~ 10 mCi) containing ≤4.9µg MK-6884	1 dose	bolus IV injection
Part II	[^{11}C]MK-6884	~ 370 MBq (~ 10 mCi) per dose, each containing ≤4.9 µg MK-6884	2 doses (at least 3 hours apart)	bolus IV injection
Part III	[^{11}C]MK-6884	~ 370 MBq (~ 10 mCi) containing ≤4.9 µg MK-6884	1 dose	bolus IV injection

ELIGIBILITY CRITERIA: Male or non-pregnant and non-breast feeding female subjects 18 to 55 years (inclusive) (Part I) and subjects 55 to 85 years (inclusive) (Parts II and III) at the pre-trial (screening) visit were eligible to enroll. Subjects in Part II were willing to allow the investigator to place an arterial catheter in the radial artery to assess if they were a good candidate for arterial catheter placement. Subjects in Part II also had a Mini Mental Status Examination (MMSE) score ≥27. Subjects in Part III were patients with moderate to severe AD (MMSE score ≤20) with a clear history of cognitive and functional decline for over at least 1 year and who were on a stable dose of an acetylcholinesterase inhibitor (AChEI) for symptomatic treatment of AD for at least 4 weeks prior to screening.

OBJECTIVES AND ENDPOINTS:

Primary Objectives	Primary Endpoints
Part I 1. To investigate the safety and tolerability of a single IV dose of [^{11}C]MK-6884 administered to healthy adult subjects. 2. To estimate the whole-body and internal organ radiation absorbed dose following administration of a single IV dose of [^{11}C]MK6884 in healthy adult subjects. **Part II** 1. To evaluate the safety and tolerability of 2 IV doses of [^{11}C]MK-6884 administered to healthy elderly subjects. 2. To evaluate [^{11}C]MK-6884 kinetics throughout	**Safety (systemic and radiation)** Systemic: assessed throughout the study by monitoring subjects for clinical adverse events (AEs), physical examinations, vital signs, 12-lead electrocardiograms (ECG) and laboratory safety tests to detect any medically meaningful effects of the tracer on physiology Radiation: whole-body PET scan estimates for [^{11}C]MK-6884 tracer radiation exposure and organ distribution (effective dose equivalent, effective dose [ED] and radiation

the brain following IV administration and to determine an index of baseline M4 receptor availability. 3. To evaluate intra-subject T-RT (test-retest) variability of the M4 receptor availability in brain following IV administration of 2 serial doses of [^{11}C]MK-6884. **Part III** 1. To investigate the safety and tolerability of a single IV dose of [^{11}C]MK-6884 administered to patients with AD. 2. To determine [^{11}C]MK-6884 regional brain distribution and index of baseline M4 receptor availability in patients with AD.	absorbed doses to individual organs) **Pharmacodynamics** • Part I: Whole-body and internal organ radiation dose evaluated by whole-body PET scans • Part II: M4 muscarinic cholinergic positive allosteric modulatory site (M4 PAM) receptor availability and intra-subject[a] variability in healthy subjects (Part II) by brain PET scan, including: (1) volume of distribution or one of its surrogates (2) T-RT variability of the volume of distribution or one of its surrogates • Part III: M4 PAM receptor availability and its inter-subject variability in patients with AD by brain PET scan, including: binding potential or one of its surrogates (Part III)
Exploratory Objective	**Exploratory Endpoints**
Part III To explore the relationship between [^{11}C]MK-6884 brain regional M4 receptor density index, peripheral acetylcholinesterase (AChE) activity, and AChEI concentration. **Parts I, II, and III[b]** To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome may be analyzed for association with clinical data collected in this study.	• Part III: AChEI as assessed by RBC-AChE activity with peripheral AChEI concentrations and [^{11}C]MK-6884 binding in patients with AD

[a] Misidentified as inter-subject variability in the protocol.
[b] Analysis of exploratory endpoints are performed at the discretion of the Sponsor; variation across the human genome was not analyzed in this study.

NUMBER OF SUBJECTS (planned and analyzed): Up to 26 subjects were planned to be enrolled. Twenty (20) subjects were actually enrolled and 19 subjects completed. One (1) subject in Part II withdrew consent for personal reasons after receiving 1 dose of study drug.

METHODS: Safety (All Parts): Incidence of AEs were descriptively summarized.

Pharmacodynamics: Part I was designed to determine the whole-body and internal organ radiation absorbed dose by collecting 9 consecutive whole-body scans in 3 subjects. 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 time-activity curves and retention of radioactivity in these regions to calculate the ED in modeling the biodistribution and elimination of [^{11}C]MK-6884.

Part II determined the kinetics of [^{11}C]MK-6884 distribution throughout the brain and determined the intra-subject T-RT variability of brain M4 PAM site availability following the administration of 2 IV doses of [^{11}C]MK-6884. The regional brain-time activity curves for all subjects were fitted by compartmental modeling, with metabolite-corrected arterial input functions to obtain the volume of distribution (V_T ,a tissue/plasma concentration ratio at equilibrium). Subsequently, target region BP_{ND} was estimated using the simplified reference tissue model (SRTM) and transient equilibrium tissue ratio (TE-TR) methods using the cerebellum as the reference region.

T-RT variability of V_T was calculated as = $2x(V_T^{scan1}-V_T^{scan2})/(V_T^{scan1}+V_T^{scan2})$ and
T-RT variability of BP_{ND} was calculated as = $2x(BP_{ND}^{scan1}-BP_{ND}^{scan2})/(BP_{ND}^{scan1}+BP_{ND}^{scan2})$.

Part III evaluated [^{11}C]MK-6884 administered to patients with moderate to severe AD to determine BP_{ND}. All patients with AD were stably maintained on an AChEI (donepezil or rivastigmine) for at least 4 weeks prior to screening. The regional brain time activity curves for all patients with AD were fitted using the cerebellum as the reference region to estimate striatal BP_{ND} with the TE-TR method. Because the striatum includes both the caudate and putamen, it constitutes a larger ROI for determining the binding signal compared to the putamen alone. Targeting the striatum will therefore provide more consistent measures of BP_{ND}. As an exploratory objective, the relationship between the regional BP_{ND} of [^{11}C]MK-6884, plasma levels of AChEI, and erythrocyte AChE activity were evaluated. The information on plasma concentration and RBC-AChE activity was used to explore quantitative relationships between BP_{ND} versus plasma concentrations of AChEI (eg, donepezil) and BP_{ND} versus RBC-AChE activity using regression analysis or non-linear mixed-effect modeling.

RESULTS:

Disposition, Demographics and Baseline Characteristics:

Subject Characteristics for Public Disclosure

	MK-6884 (Part I)		MK-6884 (Part II)		MK-6884 (Part III)		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	3		7		10		20	
Gender								
Male	2	(66.7)	5	(71.4)	5	(50.0)	12	(60.0)
Female	1	(33.3)	2	(28.6)	5	(50.0)	8	(40.0)
Age (Years)								
Newborns (0-27 days)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infants and toddlers (28 days - 23 months)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Children (2-11 years)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Adolescents (12-17 years)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Adults (between 18 and 64 years)	3	(100.0)	5	(71.4)	3	(30.0)	11	(55.0)
From 65 to 84 years	0	(0.0)	2	(28.6)	7	(70.0)	9	(45.0)
85 years and over	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Mean	25.3		62.6		67.6		59.5	
SD	2.1		5.4		5.2		15.6	
PPD								
Race								
PPD								
Ethnicity								
PPD								

Subject Characteristics for Public Disclosure

	MK-6884 (Part I) n	(%)	MK-6884 (Part II) n	(%)	MK-6884 (Part III) n	(%)	Total n	(%)
Ethnicity								
PPD								
MMSE								
Subjects with data	0		7		10		17	
Mean			29		14		20	
SD			1		6		9	
Median			29		15		20	
Range			28 to 30		3 to 20		3 to 30	

Part I Treatment: HS single intravenous (IV) dose of ~ 133-360 MBq (~ 3.6-9.7 mCi, ≤ 4.9 µg)
Part II Treatment: HES 2 separate single IV doses of ~ 161-358 MBq (~ 4.3-9.7 mCi, ≤ 4.9 µg)
Part III Treatment: AD single IV dose of ~ 325-479 MBq (~ 8.8-13 mCi, ≤ 4.9 µg)
AD=patient with Alzheimer´s Disease (55 to 85 years, inclusive)
HES=healthy elderly subject (55 to 85 years, inclusive)
HS= healthy subject (18 to 55 years, inclusive)
MMSE = mini mental status examination

Source: [P001V01MK6884: analysis-adsl]

Number of subjects randomized/treated/ongoing/discontinued:

Disposition of Subjects

	MK-6884 (Part I) n	(%)	MK-6884 (Part II) n	(%)	MK-6884 (Part III) n	(%)	Total n	(%)
Subjects in population	3		7		10		20	
Trial Disposition								
Completed	3	(100.0)	6	(85.7)	10	(100.0)	19	(95.0)
Discontinued	0	(0.0)	1	(14.3)	0	(0.0)	1	(5.0)
Withdrawal By Subject	0	(0.0)	1	(14.3)	0	(0.0)	1	(5.0)

Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.
Part I Treatment: HS single intravenous (IV) dose of ~ 133-360 MBq (~ 3.6-9.7 mCi, ≤ 4.9 µg)
Part II Treatment: HES 2 separate single IV doses of ~ 161-358 MBq (~ 4.3-9.7 mCi, ≤ 4.9 µg)
Part III Treatment: AD single IV dose of ~ 325-479 MBq (~ 8.8-13 mCi, ≤ 4.9 µg)
AD=patient with Alzheimer´s Disease (55 to 85 years, inclusive)
HES=healthy elderly subject (55 to 85 years, inclusive)
HS= healthy subject (18 to 55 years, inclusive)

Source: [P001V01MK6884: analysis-adsl] [P001V01MK6884: tabulations-dsplus]

Radiation Safety and Tracer Kinetics:

- Dosimetry (Part I)
  [^{11}C]MK-6884 was widely distributed to various body organs. The ED for [^{11}C]MK-6884 was 7.20 ± 1.27 µSv/MBq [Table 1], which is typical of [^{11}C]-labeled tracers. The administration of a single 300 MBq dose of [^{11}C]MK-6884 for PET/CT scanning is anticipated to result in a total human ED of about 2.2 mSv. Based on the acceptable annual radiation limit (ED <10 mSv) for healthy subjects, the human dosimetry of

[^{11}C]MK-6884 would allow up to 4 PET scans/subject per year (each dose ≤260 MBq [7.0 mCi]).

- Tracer Kinetics and Test-retest Variability (Part II)
  The kinetics of [^{11}C]MK-6884 distribution were investigated in Part II. The rate of brain uptake was moderate, peaking very early (<3 min) after injection, with an average peak standardized uptake value (SUV) of 2.5 [Figure 1; top]. The brain region rank order of tracer uptake was putamen > cortex > cerebellum [Figure 1, bottom]. The tracer was rapidly cleared from all brain regions, with a rank order of clearance of cerebellum > cortex > putamen. For compartmental modeling, a 1-tissue compartment model did not provide a good fit to PET data. The fit of the conventional 2-tissue compartment model to the data was improved, but could not yield stable V_T estimates for the brain regions analyzed. Given consideration of potential radiolabeled, brain-penetrant metabolites, an independent compartment was added to the conventional 2-tissue compartment model. This revised model provided both an excellent fit to the PET data and stable V_T estimates in all brain regions [Table 2]. The SRTM did not provide a reasonable fit to the data (BP_{ND}: 0.97 ± 0.11 for putamen, 0.76 ± 0.13 for striatum, n=6); the TE-TR method provided a BP_{ND} value of 1.15 ± 0.14 for the putamen and 0.96 ± 0.13 for the striatum [Table 3].

  The T-RT variability for V_T was acceptable, with the variability associated with all brain regions analyzed within 13% [Table 2]. The intra-individual T-RT variability for the BP_{ND} was ~ 14% for the putamen and ~ 11% for the striatum, as determined using the TE-TR method. In the original protocol, it was stated that an average T-RT variability of ≤20% is acceptable for a practical PET tracer.

- Tracer Evaluation in Moderate to Severe Alzheimer's disease (Part III)
  [^{11}C]MK-6884 showed good uptake in the striatum of AD patients, with a mean BP_{ND} of 0.98 ± 0.20 (n=10). This BP_{ND} was not significantly different from that of healthy elderly subjects (0.96 ± 0.13) [Figure 2] and [Table 4]. Although several patients had remarkable asymmetries in cortical uptake, striatal uptake was relatively symmetrical. In contrast, not only was [^{11}C]MK-6884 binding regionally heterogeneous in the cortex, it was lower on average in the frontal cortex of patients with AD than healthy elderly subjects (0.74 ± 0.20 and 0.92 ± 0.15, respectively). The magnitude of the BP_{ND} did not appear related to the AChEI treatment that patients with AD were receiving. However, there was insufficient data to make a statistical determination of the significance of this effect.

- The Relationship Between AChEI Concentration, AChE Activity and BP_{ND} (Part III)
  Plasma AChEI concentrations were analyzed following the administration of donepezil because of the preponderance of subjects treated with donepezil over rivastigmine in this study [Table 4]. The availability of the PK/PD relationships described in the scientific literature for donepezil may facilitate further data analysis.
  A negative correlation was observed with AChE activity in RBC and the donepezil concentration [Figure 3; Panel A]. As a consequence of peripheral AChE inhibition and assuming a similar effect is expected in brain, a higher BP_{ND} was noted in

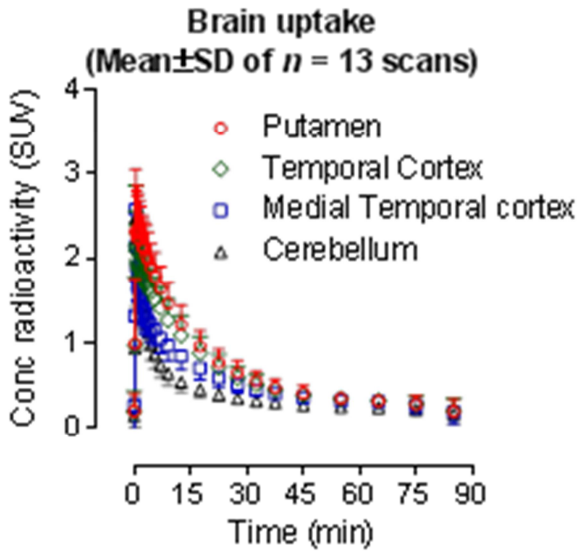
subjects with higher plasma donepezil concentrations [Figure 3; Panel B] and lower AChE activity [Figure 3; Panel C], suggesting that the magnitude of ACh tone is positively correlated with the BP_{ND} for [^{11}C]MK-6884.

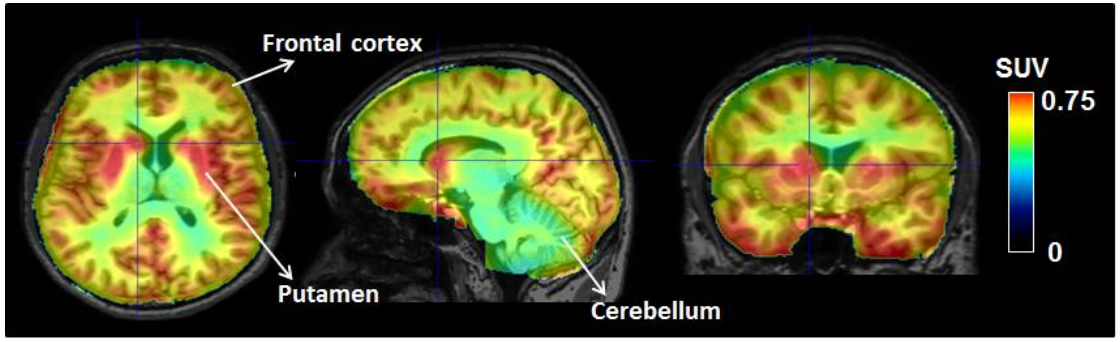
Table 1

Organ Effective Dose (mSv/MBq) of [^{11}C]MK-6884, Nuclide: C-11 (1.22E03 sec)

Target Organ	Subject 1 (female)	Subject 2 (male)	Subject 3 (male)	Average	Standard Deviation
Adrenals	1.14E-05	7.82E-06	8.49E-06	9.24E-06	1.90E-06
Brain	8.20E-06	6.14E-06	5.65E-06	6.66E-06	1.35E-06
Breasts	1.01E-04	5.86E-05	8.15E-05	8.04E-05	2.12E-05
Gallbladder Wall	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
LLI Wall	6.54E-04	3.63E-04	4.81E-04	4.99E-04	1.46E-04
Small Intestine	1.04E-03	6.15E-04	7.50E-04	8.02E-04	2.17E-04
Stomach Wall	4.59E-04	2.68E-04	3.44E-04	3.57E-04	9.62E-05
ULI Wall	3.97E-05	2.43E-05	2.96E-05	3.12E-05	7.82E-06
Heart Wall	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Kidneys	4.86E-05	5.28E-05	4.15E-05	4.76E-05	5.71E-06
Liver	1.28E-03	1.03E-03	8.09E-04	1.04E-03	2.36E-04
Lungs	9.71E-04	5.55E-04	6.00E-04	7.09E-04	2.28E-04
Muscle	6.84E-06	3.96E-06	5.44E-06	5.41E-06	1.44E-06
Ovaries	1.26E-03			1.26E-03	
Pancreas	1.18E-05	7.67E-06	8.68E-06	9.38E-06	2.15E-06
Red Marrow	5.93E-04	4.83E-04	5.48E-04	5.41E-04	5.53E-05
Osteogenic Cells	5.21E-05	3.09E-05	4.01E-05	4.10E-05	1.06E-05
Skin	1.82E-05	1.01E-05	1.51E-05	1.45E-05	4.09E-06
Spleen	4.87E-05	1.12E-05	1.68E-05	2.56E-05	2.02E-05
Testes		1.29E-03	2.10E-03	1.70E-03	5.73E-04
Thymus	5.78E-06	3.43E-06	4.68E-06	4.63E-06	1.18E-06
Thyroid	8.96E-05	4.85E-05	8.16E-05	7.32E-05	2.18E-05
Urinary Bladder Wall	1.86E-03	1.16E-03	1.02E-03	1.35E-03	4.50E-04
Uterus	1.60E-05	9.43E-06	1.17E-05	1.24E-05	3.34E-06
Effective Dose (mSv/MBq)	**8.56E-03**	**6.04E-03**	**7.00E-03**	**7.20E-03**	**1.27E-03**

Figure 1
Time Activity Curves of [^{11}C]MK-6684 in Human Brain (top) and Average PET Image (10 - 90 min) Fused to Same Subject's MRI after Injection of [^{11}C]MK-6884 in a Healthy Subject (bottom)





Each pixel of PET image is scaled according to the SUV color bar on the right.

Table 2

PET Total Distribution Volume (V_T) Estimates From Representative Brain Regions, (n=6)

Regional V_T (mL/cm^3)	Compartmental Modeling		
	Test	**Retest**	**TRV (%)**
Putamen	1.00± 0.25	0.98± 0.16	12.9± 5.8
Frontal cortex	0.84± 0.21	0.78± 0.13	12.6± 7.6
Temporal cortex	0.83± 0.21	0.79± 0.14	11.9± 8.7
Hippocampus	0.58± 0.18	0.58± 0.12	12.1± 9.6
Cerebellum	0.39± 0.10	0.41± 0.07	12.1± 9.1

V_T Test-retest Variability (TRV) calculated based on 6 elderly healthy subjects in Protocol Number 001 Part 2 as: $TRV = 2 \times \frac{\left|V_T^{scan1} - V_T^{scan2}\right|}{V_T^{scan1} + V_T^{scan2}}$.

Table 3

Non-displaceable Binding Potential Estimates From Representative Brain Regions With Simplified Reference Tissue Model and Transient Equilibrium Tissue Ratio Methods, (n=6)

Regional BP_{ND}	SRTM			Transient Equilibrium Tissue Ratio		
	Test	**Retest**	**TRV(%)**	**Test**	**Retest**	**TRV(%)**
Putamen	0.97± 0.11	0.92± 0.16	15.5± 9.4	1.15± 0.14	1.16± 0.20	14.1± 9.0
Striatum	0.76± 0.13	0.70± 0.18	19.9± 14.2	0.96 ± 0.13	1.00± 0.18	11.1± 9.2
Frontal cortex	0.73± 0.11	0.66± 0.17	17.9± 12.9	0.92± 0.15	0.86± 0.19	16.0± 7.8
Temporal cortex	0.73± 0.10	0.66± 0.15	16.3± 12.9	0.92± 0.12	0.83± 0.17	10.9± 13.7
Hippocampus	0.34± 0.09	0.28± 0.10	33.8 ± 23.1	0.45± 0.11	0.37± 0.10	24.9 ± 15.3

BP_{ND}=non-displaceable binding potential; TE-TR= transient equilibrium tissue ratio; TRV=test-retest variability; SRTM=simplified reference tissue model.

Figure 2

Representative PET Scans of [^{11}C]MK-6884 in Healthy Elderly Subjects (Matched by Age and Gender) to Patients With Alzheimer's Disease

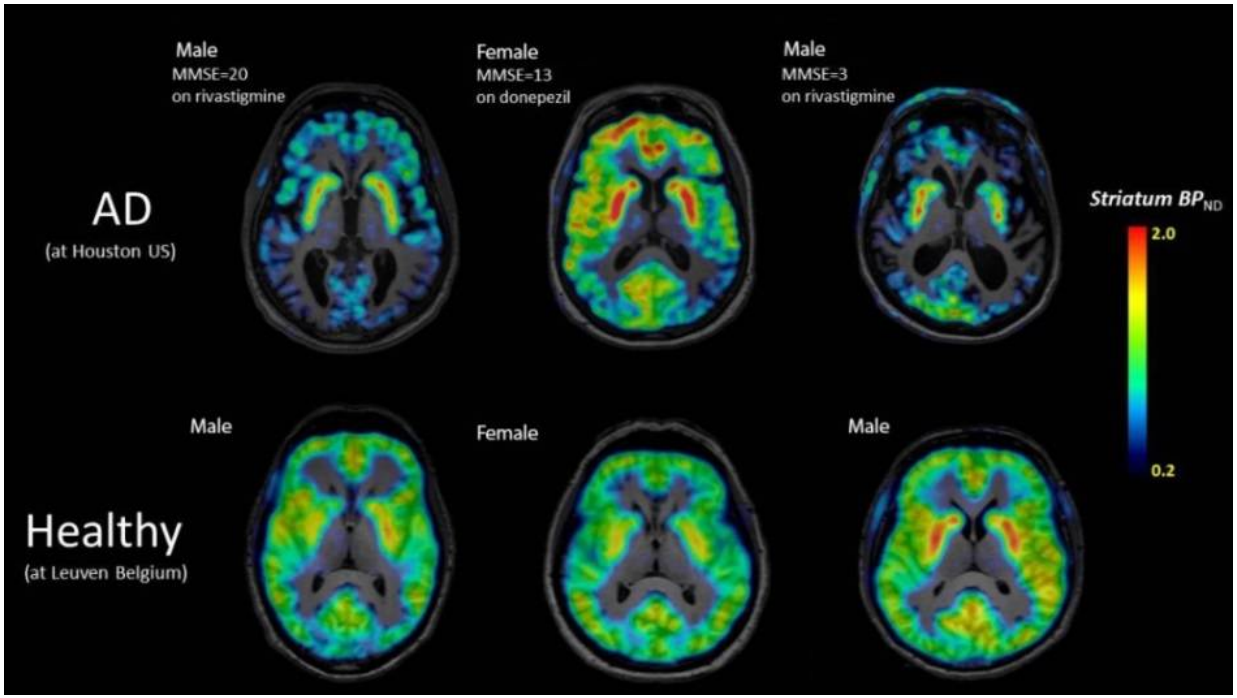


Table 4

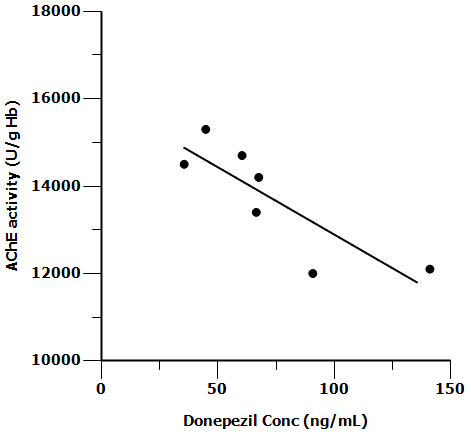
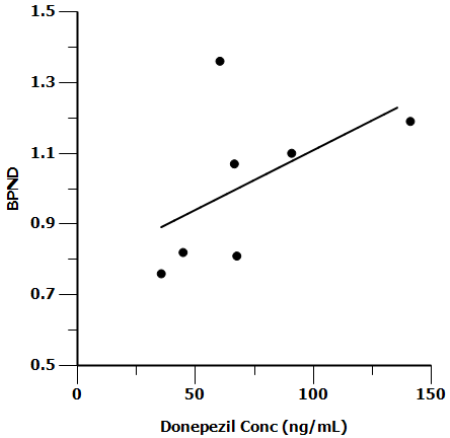
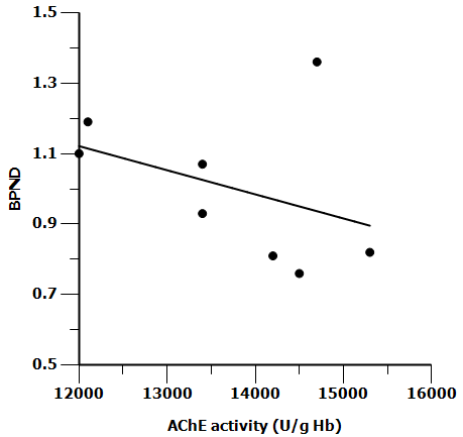
Regional Non-displaceable Binding Potential of [^{11}C]MK-6884 From Patients with Moderate to Severe Alzheimer's Disease

MMSE Score[a]	AChEI Treatment	BP_{ND} [^{11}C]MK-6884	
		Frontal Cortex	Striatum
20	Rivastigmine	0.63	0.93
14	Donepezil	1.01	1.36
3	Rivastigmine	0.46	0.95
14	Rivastigmine	0.70	0.79
12	Donepezil	0.56	0.76
6	Donepezil	0.66	0.81
18	Donepezil	1.04	1.19
16	Donepezil	0.82	1.10
20	Donepezil	0.96	1.07
18	Donepezil	0.60	0.82
Average BP_{ND} ± SD		0.74 ± 0.20	0.98 ± 0.20

[a] MMSE scores are from individual subjects tested in Part III of the study.
AChEI = acetylcholinesterase inhibitor
AD = patient with Alzheimer´s Disease
BP_{ND} = non-displaceable binding potential
MMSE= mini mental status examination
SD = standard deviation

Figure 3

Relationships Between Donepezil (DPZ) Concentration, Acetylcholinesterase (AChE) Activity and Non-displaceable Binding Potential (BP_{ND})

Panel A	Panel B	Panel C
		
AChE activity = 15970 + DPZ concentration x -30.1	BP_{ND} = 0.77 + DPZ concentration x 0.00338	BP_{ND} = 1.94 + AChE activity x -0.0000684

Safety:

- Overall, of the 20 subjects included in the safety analysis, 7 (35%) experienced 1 or more AEs during the study.
- The subjects in the study reporting one or more non-serious AEs are: n=1 (33.3%) in Part I, n=4 (57.1%) in Part II, and n=1 (10%) in Part III [Table 5].
- There was one serious adverse event (SAE) reported in Part II [Table 6]. A subject reported a tendon rupture due to a bike accident on Day 3, 2 days after receiving 2 doses of [^{11}C]MK-6884 (162 MBq [4.4 mCi] and 331 MBq [9.0 mCi]). The SAE was judged by the investigator to be severe but not related to study treatment. The subject recovered with sequelae upon follow-up at 3 months after the incident occurred.
- One (1; 5%) subject in Part II of the study reported an AE that was determined by the investigator to be drug related. The subject experienced mild glossodynia that lasted 20 minutes in duration after receiving the first [^{11}C]MK-6884 dose of 346 MBq (9.3 mCi) on Day 1. The episode of glossodynia resolved before the subject was discharged from the study.
- There were no deaths or events of clinical interest reported.
- No subject discontinued from the study due to an AE.
- There were no clinically meaningful trends observed as a function of treatment for laboratory safety tests, vital signs, or ECGs.

Table 5

Subjects With Non-serious Adverse Events For Disclosure to Public Databases (Incidence > 0% in One or More Treatment Groups)

	MK-6884 (Part I)			MK-6884 (Part II)			MK-6884 (Part III)		
	n	(%)	Number of Events	n	(%)	Number of Events	n	(%)	Number of Events
Subjects in population	3			7			10		
with one or more non-serious adverse events that met the incidence cutoff	1	(33.3)	4	4	(57.1)	8	1	(10.0)	1
with no non-serious adverse events that met the incidence cutoff	2	(66.7)		3	(42.9)		9	(90.0)	
Gastrointestinal disorders									
Abdominal pain upper	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0
Dry mouth	0	(0.0)	0	0	(0.0)	0	1	(10.0)	1
Dyspepsia	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0
Glossodynia	0	(0.0)	0	1	(14.3)	1	0	(0.0)	0
Lip dry	0	(0.0)	0	1	(14.3)	1	0	(0.0)	0
Nausea	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0
General disorders and administration site conditions									
Catheter site pain	0	(0.0)	0	1	(14.3)	1	0	(0.0)	0
Influenza like illness	0	(0.0)	0	1	(14.3)	1	0	(0.0)	0
Injury, poisoning and procedural complications									
Procedural nausea	0	(0.0)	0	1	(14.3)	1	0	(0.0)	0

Subjects With Non-serious Adverse Events For Disclosure to Public Databases (Incidence > 0% in One or More Treatment Groups)

	MK-6884 (Part I)			MK-6884 (Part II)			MK-6884 (Part III)		
	n	(%)	Number of Events	n	(%)	Number of Events	n	(%)	Number of Events
Musculoskeletal and connective tissue disorders									
Pain in extremity	1	(33.3)	1	0	(0.0)	0	0	(0.0)	0
Nervous system disorders									
Dizziness	0	(0.0)	0	1	(14.3)	1	0	(0.0)	0
Dizziness postural	0	(0.0)	0	1	(14.3)	1	0	(0.0)	0
Skin and subcutaneous tissue disorders									
Ecchymosis	0	(0.0)	0	1	(14.3)	1	0	(0.0)	0

Every subject is counted a single time for each applicable non-serious adverse event. Serious adverse events are not counted in this report.

A specific non-serious adverse event appears on this report only if its incidence in one or more of the columns is greater than the percent incidence specified in the report title, prior to rounding. A system organ class appears on this report only if one or more specific non-serious adverse events in that system organ class appear on this report.

Part I Treatment: HS single intravenous (IV) dose of ~ 133-360 MBq (~ 3.6-9.7 mCi, ≤ 4.9 µg)

Part II Treatment: HES 2 separate single IV doses of ~ 161-358 MBq (~ 4.3-9.7 mCi, ≤ 4.9 µg)

Part III Treatment: AD single IV dose of ~ 325-479 MBq (~ 8.8-13 mCi, ≤ 4.9 µg)

AD=patient with Alzheimer´s Disease (55 to 85 years, inclusive)

HES=healthy elderly subject (55 to 85 years, inclusive)

HS= healthy subject (18 to 55 years, inclusive)

Adverse event terms are from MedDRA Version 20.1

Source: [P001V01MK6884: analysis-adsl] [P001V01MK6884: tabulations-aeplus]

Table 6

Subjects With Serious Adverse Events For Disclosure to Public Databases (Incidence > 0% in One or More Treatment Groups)

	MK-6884 (Part I)			MK-6884 (Part II)			MK-6884 (Part III)		
	n	(%)	Number of Events	n	(%)	Number of Events	n	(%)	Number of Events
Subjects in population	3			7			10		
with one or more serious adverse events	0	(0.0)	0	1	(14.3)	1	0	(0.0)	0
with no serious adverse events	3	(100.0)		6	(85.7)		10	(100.0)	
Injury, poisoning and procedural complications									
Tendon rupture	0	(0.0)	0	1	(14.3)	1	0	(0.0)	0

Every subject is counted a single time for each applicable serious adverse event.
A system organ class appears on this report only if one or more specific serious adverse events in that system organ class appear on this report.
Part I Treatment: HS single intravenous (IV) dose of ~133-360 MBq (~3.6-9.7 mCi, ≤ 4.9 µg)
Part II Treatment: HES 2 separate single IV doses of ~ 161-358 MBq (~4.3-9.7 mCi, ≤ 4.9 µg)
Part III Treatment: AD single IV dose of ~ 325-479 MBq (~8.8-13 mCi, ≤ 4.9 µg)
AD=patient with Alzheimer´s Disease (55 to 85 years, inclusive)
HES=healthy elderly subject (55 to 85 years, inclusive)
HS= healthy subject (18 to 55 years, inclusive)
Adverse event terms are from MedDRA Version 20.1

Source: [P001V01MK6884: analysis-adsl] [P001V01MK6884: tabulations-aeplus]

CONCLUSIONS:

- Single IV doses of [^{11}C]MK-6884 (up to ~ 479 MBq [~ 13.0 mCi]) were administered to healthy subjects and patients with AD, while 2 IV doses (up to ~ 358 MBq [~ 9.7 mCi]) were administered to healthy elderly subjects; all doses were generally well-tolerated and provided no indication of clinically significant radiochemical toxicity or undue radiation risks.
- Dosimetry calculations from healthy subjects support up to 4 [^{11}C]MK-6884 injections in humans per year (each dose ≤260 MBq [7.0 mCi]).
- The rank order of tracer uptake by brain region was putamen > cortex > cerebellum. The striatum was targeted as the primary ROI in the basal ganglia (as opposed to the caudate and putamen being analyzed separately) because of its ability to provide more consistent measures of BP_{ND}. This was based on: the inclusion of both the caudate and putamen in the striatum; the quantitative similarity of the BP_{ND} of the putamen and striatum; and the size of the striatum, which constitutes a larger ROI for determining the binding signal compared to the putamen alone.

- The average intra-subject test-retest variability for the BP_{ND} determined by [^{11}C]MK-6884 PET imaging is acceptable (≤20%).
- The observed values of T-RT variability associated with either the BP_{ND} or V_T are within the limits of acceptability for a quantitative assessment of baseline BP_{ND} and of target engagement. In addition, the striatum, consisting of both the caudate and putamen, provided robust BP_{ND} estimates that were used to evaluate binding in patients with AD, in lieu of measures using the putamen alone.
- [^{11}C]MK-6884 demonstrated a regional mean BP_{ND} of 0.98 ± 0.20 (n=10) in the striatum of patients with AD. This value did not differ from the BP_{ND} in healthy elderly subjects (0.96 ± 0.13) (n=6).
- The BP_{ND} of [^{11}C]MK-6884 in the frontal cortex was lower on average in patients with AD than healthy elderly subjects (0.74 ± 0.20 and 0.92 ± 0.15, respectively), indicating that the density of target M4 receptors in the striatum is unaffected by AD pathology and support the potential utility of M4 PAMs in treating the neuropsychiatric symptoms of dementia in patients with AD.
- Acceptable T-RT variability, high uptake into the striatum, and similarity in striatal BP_{ND} between healthy elderly participants and patients with AD supports the use of [^{11}C]MK-6884 as a PET tracer for investigating the status of M4 PAM sites in select brain regions.

PUBLICATIONS: As of the date of this report, there are no publications based on this study.

REPORT DATE: 16-MAY-2018