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TITLE:

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

IND NUMBER: 127,788
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.1.3	Subject Exclusion Criteria: Part III	Updated exclusion criterion # 19 regarding prior exposure to radiation to exclude subjects who underwent a radiological exam with a radiation burden exceeding 30 mSv (change from 10 mSv).	Updated eligibility criterion to align with the level of radiation burden associated with radiological exams typically conducted at the Part III trial site. This change was made to expand on the potential pool of study participants who are under the care of the Part III trial investigator.
6.1.3	Trial Flow Chart Part III	Removal of predose urine/blood drug screen and footnote "h" associated with this procedure	Removed non-critical study procedure to reduce unnecessary burden on Alzheimer's Disease (AD) study participants. Based on the nature of the study population, it is expected that any negative drug screen test results from the Screening Visit will not change prior to dosing for subjects already deemed eligible for the trial.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.2.2	Rationale for Dose Selection/ Regimen/Modification	Updated to include acceptable yearly limit (Effective Dose [ED] <50 mSv) for radiation exposure in the US.	Update to reflect acceptable annual limits for radiation dose in the geographic region where Part III is to be conducted.
6.1.3	Trial Flow Chart Part III	For footnotes "b" and "c" pertaining to the timing of vital signs and ECG measurements, the timing for end of scanning session is corrected to read "(~90 minutes post-dose)" instead of "(~2 hours post-dose)".	Correction to align with PET scan duration (up to ~ 90 minutes) planned for Part III
7.1.4.3	Domiciling	Clarification that subjects in Part III of the study will report to the research center on Day 1 (whereas subjects in Part I of the study will report to the research center on Day -1)	Update to reflect operational logistics/study conduct at Part III trial site
7.1.5.1	Screening (Part I, Part II and Part III)	Clarified that screening can occur within the 4 week visit window.	Clarification on timing of screening procedures
7.1.5.2	Treatment Period (Part I, Part II, and Part III)	For Part III, Table 7 Clarified the sequence of procedures related to blood collections	Update to reflect operational logistics/study conduct at Part III trial site

1.0 TRIAL SUMMARY

Abbreviated Title	[^{11}C]MK-6884 Positron Emission Tomography Tracer Validation Trial
Trial Phase	Phase I
Clinical Indication	Alzheimer's Disease (AD)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous (IV)
Trial Blinding	Unblinded Open-label
Treatment Groups	Part I: Single IV dose of approximately 370 MBq (~10 mCi, ≤ 4.9 µg) [^{11}C]MK-6884 (healthy subjects) Part II: Two separate IV doses of approximately 370 MBq (~10 mCi, ≤ 4.9 µg) per dose [^{11}C]MK-6884 (healthy elderly subjects) Part III: Single IV dose of approximately 370 MBq (~10 mCi, ≤ 4.9 µg) [^{11}C]MK-6884 (moderate to severely impaired Alzheimer's Disease patients)
Number of trial subjects	Up to 26 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 20 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 6-7 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact (Parts I-III). After a screening phase of 4 weeks, each subject will be receiving assigned treatment for approximately 1 day (Parts I and III) or up to 2 days (Part II). After the end of treatment each subject will be followed for approximately 14 days for post study evaluation (Parts I-III).

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, 3-part study in healthy subjects (Parts I and II) and moderate to severely impaired Alzheimer's disease (AD) patients (Part III) to be conducted in conformance with Good Clinical Practices. The objective of the study is to investigate the safety and utility of [^{11}C]MK-6884 as a research probe for quantifying regional receptor density of M4 muscarinic acetylcholine Positive Allosteric Modulators (PAMs) in the brain by Positron Emission Tomography (PET). All aspects of this study have been designed to qualify for conduct as a "microdose" study in accordance with ICH M3 (R2).

Only tracer doses (≤ 4.9 µg/dose) of [^{11}C]MK-6884 will be administered during this investigation. No other drugs or chemical substances will be administered (except lidocaine for arterial catheter insertion).

Part I

Part I is designed to investigate the safety and tolerability of [^{11}C]MK-6884 and to estimate the radiation absorbed per unit of administered radioactivity in the whole body and internal organs of healthy subjects. A single previously defined (IV dose of ~370 MBq (~10 mCi, ≤ 4.9 µg) [^{11}C]MK-6884 will be administered to subjects (estimate based on Rhesus study, not confirmed in human) followed by a series of whole body PET scans, clinical examinations and laboratory safety evaluations. [^{11}C]MK-6884 radiation doses for subsequent subjects may be adapted upwards or downwards after analysis of the actual dosimetry results of the initial subject(s), but will not exceed acceptable yearly limits for radiation exposure (see Section 7.1.5.5 for further details on adaptation of doses). A minimum of 3 subjects will be tested in Part I, but up to 3 additional subjects may be tested at the discretion of the investigator and Sponsor, if necessary (e.g., unexpected levels of variability, technical problems, etc).

Part II

Part II will only initiate if the Investigator and Sponsor agree there are no indications of medically meaningful radiochemical toxicity or undue radiation risks after an initial review of safety data from Part I (including clinical, clinical laboratory and radiation safety data). Part II [^{11}C]MK-6884 radiation doses may be adapted if indicated, based on actual data found during Part I (see Section 7.1.5.5 for further details on adaptation of doses).

Part II will begin the process of validating and qualifying [^{11}C]MK-6884 as a M4 PAM tracer in humans. The parameter of interest to be quantified from the PET baseline scans will be nondisplaceable binding potential (BP_{ND}) or distribution volume (V_T), an index of receptor availability. If needed, additional methods may also be employed, to more robustly characterize the tracer kinetics in both healthy and AD subjects. The possibility of reliably quantifying M4 receptor availability will be determined by measurement of the intra-subject baseline test-retest [T-RT] variability or within-subject coefficient of variation. A baseline magnetic resonance imaging (MRI) scan of the brain will be obtained for region-of-interest (ROI) delineation. Subjects will be administered 2 separate single IV doses of approximately 370 MBq (10 mCi, ≤ 4.9 µg) [^{11}C]MK-6884 with a brain PET/CT scan performed after each dose. PET images of the brain will be obtained for up to approximately 90 minutes after each administration of [^{11}C]MK-6884. There will be a wash-out of at least 3 hours between each drug administration to allow for most of the radioactivity from the first scan to decay prior to starting the second scan. In case of technical difficulties, the duration between the two scans may be adjusted at the investigator's discretion. A minimum of 6 subjects will be tested in Part II. Up to 4 additional subjects may be tested if unexpected levels of variability are observed in the first 6 subjects of Part II.

Part III

In parallel with Part II, Part III will begin the process of validating and qualifying [^{11}C]MK-6884 as a M4 PAM PET tracer in AD patients based on the results of Part I and in comparison to an age matched population of healthy elderly subjects in Part II (i.e., the AD patients enrolled in Part III will be in the same age range [55 to 85 years of age, inclusive] as

the healthy elderly subjects enrolled into Part II). Specifically, Part III will initiate upon completion of at least 3 healthy subjects in Part II for the validation of a reference region approach. A baseline MRI scan of the brain will be obtained for ROI delineation and to ensure the MRI scan is consistent with a diagnosis of moderate to severe AD. A cohort of up to 10 (target N=7 completing) moderate to severely impaired AD patients will be administered a single IV dose of approximately 370 MBq (10 mCi, ≤ 4.9 μg) [^{11}C]MK-6884. A single brain scan will be performed after the dose, and positron emission images of the brain will be obtained for approximately 90 minutes after the administration of [^{11}C]MK-6884 to verify the BP_{ND} of the [^{11}C]MK-6884 ligand. The scan duration can be shortened to approximately 60 minutes in the event that the AD patient cannot endure the 90 minutes scan..

Parts I, II, and III

Each part will be conducted with separate study populations (up to 6 healthy subjects for Part I; up to 10 elderly healthy subjects for Part II; up to 10 AD patients for Part III).

Clinical and laboratory safety evaluations will be performed up to ~3 hours following administration of each dose of [^{11}C]MK-6884. In Part I, venous blood sampling will be performed during the PET scans for optimization of methods for measurement of the radiolabeled tracer metabolites. In Part II, arterial blood sampling for measurement of the radioligand concentration (and its metabolites) will be performed during the PET scans in order to quantify the tracer kinetic modeling methods. This method utilizes an input function and will enable assessment of the possibility of performing the quantitative analysis of [^{11}C]MK-6884 in subsequent studies without the need for arterial blood sampling. The 2 doses of [^{11}C]MK-6884 for scans 1 and 2 will be separated by sufficient time to allow for most of the radioactivity from the first scan to decay prior to starting the second scan. Scans 1 and 2 will be performed on the same day or on separate (preferably consecutive) days. In case of technical difficulties, the duration between the two scans may be adjusted at the investigator's discretion. Imaging analysis will be initiated upon the completion of the first 3 healthy subjects. If the reference region is validated to accurately assess tracer binding (BP_{ND}) and there is no need for continued arterial line monitoring of radioligand concentration and its metabolites, arterial blood sampling for measurement of radioactivity concentration and its metabolites will not be performed during the scanning session following administration of [^{11}C]MK-6884 for the rest of the Part II subjects. A minimum of 6 subjects will be tested in Part II, but this part has also been designed with some flexibility to allow for dosing of up to 4 additional subjects if unexpected levels of noise or variability are observed in the first 6 subjects of Part II.

In each Part, final clinical assessment will be conducted either shortly after the completion of the final scan (i.e., the second scan in Part II) or just prior to discharge which may be at ~ 24 hours post final dose (if the subject is kept overnight at the investigator’s discretion). All adverse experiences will be reported from the signing of the informed consent through 14 days post final dose. Assessment for potential adverse experiences will be conducted at ~24 hours post dose either by phone or at the clinic, followed by an additional phone call conducted at 14 days post final dose. See Section 6.0 for additional details.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

Because this is a Phase I assessment of MK-6884 in humans, the pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being elucidated. This protocol is therefore written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Please refer to Section 7.1.5 – Visit Requirements for examples of modifications permitted within the protocol parameters.

2.2 Trial Diagram

The trial design is depicted in Figure 1, Figure 2, Figure 3, and Table 1.

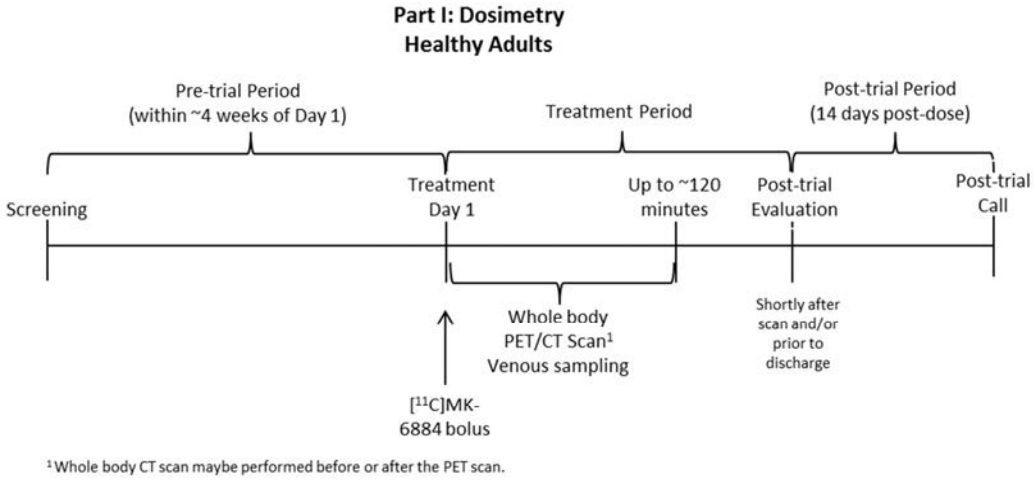


Figure 1 Study Design Part I

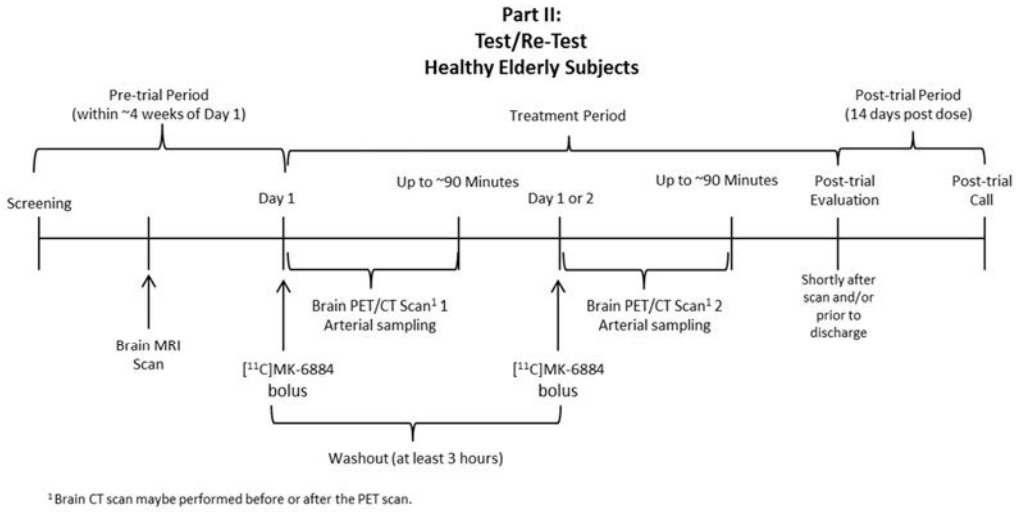


Figure 2 Study Design Part II

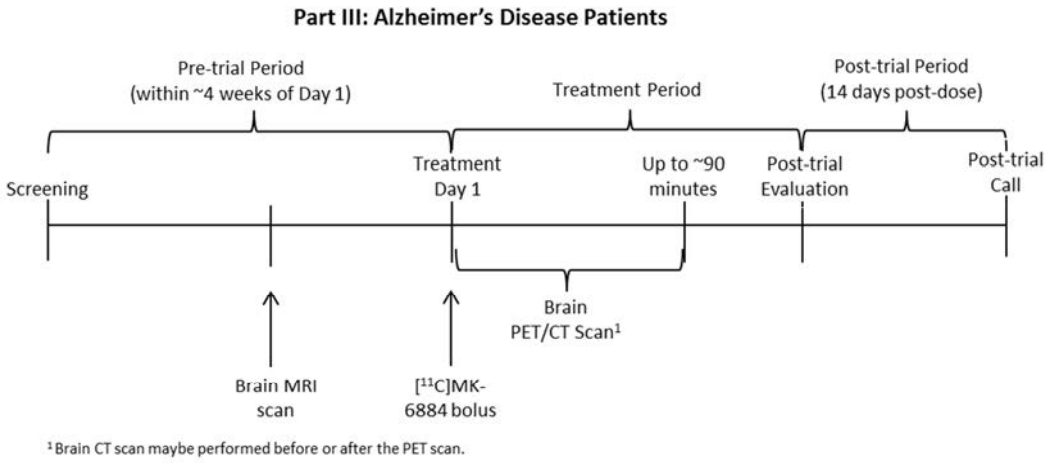


Figure 3 Study Design Part III

Table 1 Study Design Scheme

Part I[a]				
	Single IV dose of [^{11}C]MK-6884		Whole Body PET scan	
Part II[a,b]				
Brain MRI scan	Single IV dose of [^{11}C]MK-6884	Brain PET scan	Single IV dose of [^{11}C]MK-6884[c]	Brain PET scan
Part III[a,b]				
Brain MRI scan	Single IV dose of [^{11}C]MK-6884		Brain PET scan	

[a] Up to 26 subjects (Parts I, II, and III) will be allocated to receive [^{11}C]MK-6884. A single subject may only participate in one Part of the study.
[b] The suggested dose in Parts II and III may be adjusted based on evaluation of safety, tolerability and radiation dosimetry data from Part I.
[c] The second IV dose of [^{11}C]MK-6884 will be administered at least 3 hours following the first administration.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Part I

1) **Objective:** To investigate the safety and tolerability of a single intravenous dose of [^{11}C]MK-6884 administered to healthy adult subjects.

2) **Objective:** To estimate the whole body and internal organ radiation absorbed dose following administration of a single intravenous dose of [^{11}C]MK-6884 in healthy adult subjects.

   Hypothesis: Dosimetry calculations based on Part 1 data will support multiple [^{11}C]MK-6884 injections in humans.

Part II

1) **Objective:** To evaluate the safety and tolerability of two intravenous doses of [^{11}C]MK-6884 administered to healthy elderly subjects.

2) **Objective:** To evaluate [^{11}C]MK-6884 kinetics throughout the brain following intravenous administration and determine an index of baseline M4 receptor availability.

3) **Objective**: To evaluate intra-subject T-RT variability of the M4 receptor availability in brain following intravenous administration of two serial doses of [^{11}C]MK-6884.

   Hypothesis: The average intra-subject T-RT variability of M4 receptor density index measured from [^{11}C]MK-6884 PET data is acceptable ($\leq$ 20%).

Part III

1) **Objective:** To investigate the safety and tolerability of a single intravenous dose of [^{11}C]MK-6884 administered to AD patients.

2) **Objective:** To determine [^{11}C]MK-6884 regional brain distribution and index of baseline M4 receptor availability in AD patients

3.2 Secondary Objective(s) & Hypothesis(es)

There are no secondary objectives (or hypotheses) for this study.

3.3 Exploratory Objective

Parts I, II, and III

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 only

To explore the relationship between [^{11}C]MK-6884 brain regional M4 receptor density index, peripheral AChE activity, and AChEI concentration

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-6884.

Modulating the cholinergic system by specifically targeting the M4 muscarinic acetylcholine receptor (mAChR) is a novel approach to treat behavioral and perhaps certain cognitive symptoms in patients with Alzheimer's disease (AD) and schizophrenia (SCZ). Clinical studies using xanomeline (a M1/M4 preferring mAChR agonist) have established that

targeting the muscarinic cholinergic system is a viable treatment for alleviating psychosis and behavioral disturbance symptoms in AD [1] and SCZ patients [2]. However, xanomeline, like other muscarinic agonists, ultimately failed in clinical development due to lack of adequate receptor subtype selectivity resulting in adverse side effects by activation of peripheral mAChRs. The development of an M4 PAM may overcome the challenges of developing selective orthosteric muscarinic agonists.

Preclinical data have demonstrated that the binding affinity of a PAM to the target is directly dependent on the endogenous cholinergic tone, indicating the clinical utility of such a PET tracer is influenced by the level of cholinergic tone in AD. Although a substantial loss of cholinergic neurons in the cerebral cortex is an universal feature of advanced AD, histological data suggest the cholinergic neuron pathways of the striatum remain relatively intact.

An evaluation of the binding sensitivity of a M4 PAM tracer to the potential difference in cholinergic tone in AD patients will inform the clinical development of a therapeutic. [^{11}C]MK-6884, a novel PET ligand, has been preclinically qualified for target engagement of M4 PAMs and is being developed as a clinical research tool to facilitate the clinical development of M4 PAMs for AD.

4.1.1 Pharmaceutical and Therapeutic Background

[^{11}C]MK-6884 is a novel PET ligand that is being developed as a clinical research tool to facilitate the clinical development of M4 PAMs for AD. MK-6884 selectively binds to and potentiates M4 receptor at its allosteric site as a PAM, with in vitro properties suitable for an M4 PAM PET tracer: high affinity (Ki < 5 nM), moderate lipophilicity (logP < 3.5), and low susceptibility for human P-glycoprotein (P-gp) (BA/AB ratio < 2). It has been preclinically qualified for assessment of target engagement of M4 PAMs through determination of the occupancy and efficacy relationship and assessment of changes in cholinergic tone in non-human primates. [^{11}C]MK-6884 is anticipated to enable quantitative measurement of M4 receptor occupancy (RO) in the brain as a function of drug pharmacokinetics (PK).

The dosimetry and test-retest validation study with [^{11}C]MK-6884 will be the first administration of MK-6884 or [^{11}C]MK-6884 in humans. Safety pharmacology, toxicology and radiation safety studies have been performed with [^{11}C]MK-6884 in preclinical species and provide no contraindication to the initiation of clinical trials with in humans with this compound via the IV route.

[^{11}C]MK-6884 is a non-biological, small molecule, low mass, high specific activity tracer that is classified by the Food and Drug Administration (FDA) as a Type 1 radiopharmaceutical [3] and the European Union (EU) as a Class IIb radiopharmaceutical [4] and is suitable for microdosing per ICH M3(R2) guidance for PET tracers.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Preclinical PET studies show [^{11}C]MK-6884 provides a large M4 PAM specific signal in monkey brain, and *in vitro* data suggests human M4 density is sufficiently high for [^{11}C]MK-6884 to provide a useful specific signal in *in vivo* PET studies. This first

investigation in humans is an open label, three part study designed to assess whether the safety, tolerability and signal characteristics (radiation dosimetry, signal magnitude, and T-RT variability) of [^{11}C]MK-6884 support its utility to interrogate M4 PAM RO.

This 3-part study will be conducted in healthy adult male subjects and female subjects and also in age-matched moderate to severe AD patients (i.e., same age range as the healthy elderly). Each part of the study will be conducted in a separate study population. The study design for [^{11}C]MK-6884 conforms to standards in the field for measuring radiation dosimetry, baseline quantitative reproducibility (test-retest variability) and assessing radiopharmacological safety. It is intended for use in a small number of human subjects who will participate in medical research studies. It is not intended for development as a diagnostic imaging agent. It will not be developed for commercialization.

All aspects of this study have been designed to qualify for conduct as a microdose study in accordance with ICH M3 (R2) guidance.

Part I

Part I is designed to investigate the safety and tolerability of [^{11}C]MK-6884 and estimate the radiation absorbed per unit of administered radioactivity. Safety will be assessed based on series of physical examinations, vital signs, ECGs and clinical safety laboratory measurements. Radiation safety will be assessed by estimating the radiation absorbed doses per unit administered radioactivity in the whole body and its internal organs. After tracer injection, dynamic whole body PET scans will be acquired for up to 6 physical half -lives of the radioisotope [half-life of carbon-11 (^{11}C) is ~ 20 minutes]. The effective dose concentration of radioactivity in several organs will be measured as a function of time and used for radiation dose calculations. [^{11}C]MK-6884 doses for subsequent subjects may be adapted after analysis of the actual dosimetry results of the initial subject(s) in this part of the study. [^{11}C]MK-6884 administration to subsequent subjects will be separated by at least one day from the initial subject(s).

Venous blood will be drawn for metabolite assessment and the relative [^{11}C]MK-6884 fraction in plasma to optimize methods for measuring the radioactive material available for delivery to the brain.

The brain uptake information from the whole-body dosimetry scan will be used to perform an initial assessment of whether the tracer has suitable uptake in the regions of interest.

A minimum of 3 subjects will be tested in Part I, but up to 3 additional subjects may be tested, for a total of 6 subjects, if unexpected technical difficulties or levels of noise are encountered, at the discretion of the Investigator and Sponsor.

Rationale for Requirement for Mental Status Assessment of Older Subjects/Patients: Parts II and III will enroll subjects between the ages of 55 to 85 years of age (inclusive) at the first visit. To control for the potential that subjects in Part II may harbor potentially confounding minor or undocumented dementia, healthy elderly subjects enrolled in Part II must demonstrate a Mini Mental State Exam (MMSE) score ≥ 27. In Part III, the moderately

to severely impaired AD patients to be enrolled must demonstrate a MMSE score ≤ 20, in addition to other qualifying mental and physical assessments, to affirm the etiology of the patient's dementia as consistent with AD.

Part II:

Part II of this study will begin the process of validating and qualifying [^{11}C]MK-6884 as a M4 PAM tracer in humans. Part II will only be initiated if there is no indication of radiochemical toxicity, undue radiation risk or medically meaningful effect on physiology observed during Part I based on review of the safety and radiation safety data. [^{11}C]MK-6884 doses administered in Part II may be adapted to insure that the maximum exposure remains below the yearly limit of 10 mSv and within the acceptable limits for healthy human volunteers (see Section 4.2.2, Rationale for Dose Selection). The possibility of reliably quantifying M4 receptor availability will be determined by measuring the intra-subject -TRT variability. Subjects will be administered 2 separate IV doses of [^{11}C]MK-6884 separated by sufficient time (at least 3 hours) to allow most of the radioactivity from the first administration to decay prior to administering the second dose. The 2 doses will be administered preferably on the same day in order to limit the number of arterial punctures to one per evaluation. An alternate day for the second dose may be scheduled in case of technical difficulties at the discretion of the investigator.

An MRI scan of the brain will be obtained for ROI delineation. Positron emission images will be acquired for up to 2.0 hours after the administration of [^{11}C]MK-6884. It is expected that 90 minutes will be sufficient to characterize the regional cerebral tracer kinetic curves. The scanning duration may be adjusted based on available data. In addition, a CT scan, to enable attenuation correction, will be performed either before or after the PET scan. Arterial blood sampling for quantification of total radioactivity and the relative [^{11}C]MK-6884 fraction in plasma will be performed to provide a measure of radioactive material available in the brain. Arterial input function methodology is invasive and a non-invasive approach is preferable. In order to perform future studies non-invasively, a reference region (region in the brain devoid of M4 receptor) is necessary and will be assessed in this study. Clinical and laboratory safety evaluations will also be performed following administration of each dose of [^{11}C]MK-6884.

A minimum of 6 subjects will be tested in Part II, but up to 4 additional subjects may be tested, for a total of 10 subjects, if unexpected levels of noise or variability are encountered, at the discretion of the Investigator and Sponsor.

Part III:

Rationale for enrollment of moderate to severely impaired AD patients: Early work indicates the binding affinity of an M4 PAM is influenced by the endogenous receptor agonist ACh tone such that the binding affinity of a PAM increases in proportion to ambient cholinergic tone. Importantly, there may not be sufficient endogenous ACh to observe M4 PAM binding in AD, which is marked by decreased cholinergic tone in some neuronal populations as disease progresses. This risk may be mitigated to some degree by the observation that the major localization of M4 is relatively intact in the striatal regions of the

brain in AD. However, should reductions in cholinergic tone be steep in these regions, this may have a significant impact on the utility of treatment based on an M4 PAM. Nonetheless, the use of an M4 PAM to treat cognitive and behavioral symptoms of AD may be appropriate to all stages of disease, should adequate ACh tone exist to support PAM binding. Thus, AD patients with moderate to severe symptomatology will be enrolled in Part III to support evaluation of the ability a PAM to bind to the M4 receptor given the ambient ACh tone found across the range of disease severity.

Rationale for Requirement that AD Patients be Maintained on an AChEI Inhibitor: Inhibitors of acetylcholine esterase exert a cognition enhancing effect through the elevation of presynaptic acetylcholine (ACh) levels. AD patients administered such inhibitors are anticipated to possess a synaptic ACh tone that is greater than patients who are not on such inhibitors. Further, a majority of patients with moderate to severe AD symptoms are anticipated to be prescribed such inhibitors. As [^{11}C]MK-6884 is a M4 PAM whose binding potency is sensitive to ACh tone, patients administered AChEIs should offer the best potential to quantify a PET signal in such patients. Consequently, AD patients enrolled in Part III will be required to be maintained on a stable dose of a qualifying AChEI for at least 4 weeks prior to screening and throughout participation in the study. A target minimum of 3 patients stably maintained on donepezil is highly desired for enrollment to ensure that sufficient AD patients on this AChEI are investigated to support the Part III exploratory objective.

Rationale for Use of Specific AChEIs: The data obtained from AD patients on an AChEI will be used to support conclusions about ACh tone in these patients. To this end, it is reasonable to restrict the selection of AChEIs allowable at enrollment to those capable of supporting a similar level of acetylcholine esterase inhibition under normal conditions of use. Allowable AChEIs for Part III are donepezil and rivastigmine. Galantamine in particular, is not allowed as this agent harbors additional modes of interactions with the ACh signaling system that may confound the analysis of M4 PAM binding [3].

Part III Study conduct: In parallel with Part II, Part III will begin the process of validating and qualifying [^{11}C]MK-6884 as a M4 PAM PET tracer in AD patients, based on the results of Part I and in comparison to age matched (i.e., same age range from 55 to 85 years of age) healthy elderly subjects in Part II.

A baseline MRI scan of the brain will be obtained for ROI delineation and to ensure the MRI scan is consistent with a diagnosis of moderate to severe AD. Each moderate to severe AD patient enrolled in this part will be administered a single IV dose of approximately 370 MBq (~10 mCi, ≤ 4.9 μg) [^{11}C]MK-6884. A single brain scan will be performed after the dose, and positron emission images of the brain will be obtained for approximately 90 minutes after the administration of [^{11}C]MK-6884 to verify the BP_{ND} of the [^{11}C]MK-6884 ligand. The scan duration in AD patients can be shortened to approximately 60 min in the event an AD patient cannot endure the 90 minutes scan.

A minimum of 7 moderate to severely impaired AD patients will be tested in Part III, but up to 3 additional AD patients may be tested, for a total of 10 AD patients, if unexpected levels of noise or variability are encountered, at the discretion of the Investigator and Sponsor.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The radioactive dose required to produce acceptable image quality in human brain is not known. The current study will begin the process of determining if specific binding can be reliably measured at acceptable radiation doses in humans.

Nonhuman primate studies and dose selection: A pre-clinical PET study in rhesus monkey has been performed which demonstrated a high uptake of [^{11}C]MK-6884 in the brain with the largest uptake in the striatum, providing a useful specific signal. *In vitro* saturation binding studies with [^{3}H]MK-6884 in monkey and human brain striatum homogenate indicate that similar concentration (Bmax) of M4 receptors may be present in humans and therefore the human M4 PAM receptor density is sufficiently high for [^{11}C]MK-6884 to provide a useful specific signal in *in vivo* PET studies.

As directed by the eCTA Guidance [ICH Topic M3 (R2)], the total dose will not exceed 100 µgs and will not exceed 5 administrations with a washout between doses of 6 or more half-lives. Each dose will not exceed 1/100th of the NOAEL, as determined in a toxicology trial in rats after proper scaling. Dose selection for safety assessment of [^{11}C]MK-6884 was based upon assumptions of tracer specific activity and injection dose. A maximum cumulative mass associated with [^{11}C]MK-6884 to be given to a 60 kg human adult subject undergoing a single PET scan is estimated to be 4.9 µg.

A whole-body distribution PET study conducted with [^{11}C]MK-6884 in three rhesus monkeys suggest that the level of radiation absorbed should allow for multiple doses of [^{11}C]MK-6884 that may be required for clinical PET occupancy studies. Organs found to have high absorbed radiation dose included gallbladder (0.034 ± 0.020 mSv/MBq), small intestine (0.016 ± 0.016 mSv/MBq), and liver (0.014 ± 0.007 mSv/MBq). The overall ED by [^{11}C]MK-6884 was estimated to be 0.0038 ± 0.0002 mSv/MBq, which is in the typical range for ^{11}C-labeled PET tracer.

The preliminary measurement of the radiation absorbed dose from [^{11}C]MK-6884 to Standard Reference Man was estimated with data from these three nonhuman primates. Based on this, administration of one 370 MBq (10 mCi) dose or two 370 MBq (10 mCi) doses of [^{11}C]MK-6884 is predicted to result in a human Effective Dose (ED) of 1.9 mSv or 2.9 mSv, respectively (accounting for 1 WB CT resulting 0.5 mSv/scan in Part I and two head CTs resulting ~0.05 mSv/scan in Part II). Thus the radiation dose to human in the planned studies is predicted to be within acceptable yearly limits (ED < 10 mSv) for healthy subjects. This is thought to represent a dose that conforms to the As Low As Reasonably Achievable (ALARA) principle of radiation exposure. Based on pre-clinical studies this dose should provide the minimum image quality necessary to quantify tracer binding in the brain while minimizing tracer exposure for healthy subjects. This is well below the desired yearly limit of ED = 10 mSv.

[^{11}C]MK-6884 will always be administered in an open-label manner. For each scan, patients/subjects will be administered an anticipated IV dose of ≤ 4.9 µg of MK-6884 based on assumptions of a 6 mCi single injection of a tracer with minimum specific activity of 500 Ci/mmol, as explained in Section 4.2.2.1 - Maximum Doses/Exposure for This Trial. In general, cyclotron produced ^{11}C tracers have been offering specific activity much higher than

500 Ci/mmol. Therefore, the administration of 10 mCi dose of [^{11}C]MK-6884 is anticipated to result in a maximum mass dose below 4.9 µg. The actual doses that will be administered during all parts will be adjusted based on the specific activity not to exceed the maximum mass of 4.9 µg and maximum allowed radiation exposure of 10 mSv per year in Europe or 50 mSv per year in the United States.

Part I is a first-in-human study designed to investigate the safety and tolerability of [^{11}C]MK-6884 and estimate the radiation absorbed. Subjects will be administered a single IV dose of 370 MBq (10 mCi, 4.9 µg) [^{11}C]MK-6884 followed by a series of whole body PET scans, clinical examinations and laboratory safety evaluations. This dose was selected based on the results from whole-body distribution PET studies in rhesus monkeys. The selected radioactive starting dose for Part I of 370 MBq (10 mCi, 4.9 µg) per scan would result in a human ED of 1.9 mSv. The dose in Part I for subsequent subjects may be adjusted downwards or upwards based on mass dose limitation and dosimetry results learned from the initial Part I subjects.

Parts II and III will be initiated if there are no indications of medically meaningful radiochemical toxicity or undue radiation risks observed during Part I based on the initial review of safety data, including the clinical, clinical laboratory, and radiation safety data, as agreed by the Investigator and Sponsor. In Part II, subjects will receive 2 doses of [^{11}C]MK-6884. In Part III, AD patients will receive a single dose of [^{11}C]MK-6884. The administered dose in Parts II and III will be adjusted if indicated by the results from Part I.

As this is a Phase I assessment of MK-6884 in humans, and the pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. Details of allowed modifications are provided in Section 7.1.5.5 - Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters.

4.2.2.1 Maximum Dose/Exposure for This Trial

This study will be conducted under a microdosing paradigm, in accordance with the ICH M3 (R2) guidance. As per Guidance, the total dose should not exceed 100 µg and each dose should not exceed 1/100th of the NOAEL and 1/100th of the pharmacologically active dose after proper scaling.

Dose selection for safety assessment of [^{11}C]MK-6884 is based upon assumptions that a maximum cumulative mass associated with [^{11}C]MK-6884 to be given to a 60 kg human adult subject undergoing a single PET scan would be 4.9 µg. This estimate is derived from the molecular weight of MK-6884 (411.5 kD) and assumptions of a 6 mCi single injection of a tracer with minimum specific activity of 500 Ci/mmol. Therefore, the maximal single human dose for a 60 kg adult human would be 0.08 µg/kg. MK-6884 safety and toxicity studies were designed to assess up to 1000-fold margins from this maximal human single dose.

To support the safety of MK-6884, a 7-day toxicity study in rat has been performed.

MK-6884 was administered IV up to 80 µg/kg/day (1000x the maximal anticipated human dose). In this study there were no adverse effects attributed to treatment with MK-6884 at any dose. The NOAEL of 80 µg/kg/day provides a 1000-fold margin over the maximal clinical dose of 4.9 µg. This is well below the $<1/100^{th}$ of the NOEL and within the ICH M3 (R2) guidance. Thus, toxicology study results provide no contraindications to the conduct of the clinical PET studies with MK-6884.

To support that the maximal clinical MK-6884 dose of 4.9 µg is also $\leq 1/100^{th}$ of the pharmacologically active dose, an amphetamine-induced hyperactivity assay has been performed, which is a highly sensitive assay to pharmacological inhibition of M4 PAM activity. MK-6884 at 100X the projected maximal clinical single dose of 4.9 µg did not induce a significant pharmacodynamics effect in rhesus macaque in this amphetamine-induced hyperactivity model. Thus, the results of this non-clinical study support the conduct of clinical PET studies with a maximum MK-6884 dose of 4.9 µg, consistent with ICH M3(R2) guidance.

4.2.2.2 Rationale for Dose Interval and Trial Design

MK-6884, a PET tracer for non-invasive visualization of M4 PAM, is not considered a compound with higher potential for risk of harm to volunteers according to the publication "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products" (European Medicine Agency guidance released July 2007). It is not a biological molecule, does not exhibit highly species-specific action, nor is it directed towards immune system targets. Safety assessment toxicity trials and ancillary pharmacology trials with MK-6884 provide no contraindications to the initiation of clinical trials in people with this compound via the IV route. [^{11}C]MK-6884 doses for subsequent subjects may be adapted after analysis of the actual dosimetry results of the initial subject(s) in this part of the study. [^{11}C]MK-6884 administration to subsequent subjects will be separated by at least one day from the initial subject(s). No dose-limiting toxicities were observed in 7-day toxicity trials, and substantial preclinical safety margins were obtained over initial human doses.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

In order to assess the potential efficacy of [^{11}C]MK-6884 as a radiopharmaceutical tracer for M4 PAM receptor binding, the following endpoints have been selected to establish the validity and reliability of [^{11}C]MK-6884:

1. In Parts II and III, index/Indices of M4 PAM receptor availability will be determined by kinetic modeling of the dynamic PET data. Indices that may be measured include: (1) total volume of distribution (V_T); (2) non-displaceable binding potential (BP_{ND}); and/or standard uptake value ratio (SUVR). The V_T is the ratio at equilibrium of the concentration of radioligand in a region of tissue to that in plasma. V_T will be assessed using the metabolite corrected tracer plasma curve obtained from arterial blood sampling during the corresponding scan (relative [^{11}C]MK-6884 fraction in plasma), to provide a measure of the radioactive material available to the brain. BP_{ND} is the ratio at equilibrium of specifically bound radioligand to that of a non-displaceable radioligand in tissue. The measurement of BP_{ND} assumes the presence of a reference region (region in the brain devoid of M4 PAM binding site), and does not require arterial sampling. SUVR is a semi-quantitative measure of tracer uptake estimated using a reference region with low/no tracer binding. SUVR is calculated as the ratio of the average tracer uptake over a given time period in the target region relative to a reference region. In order to perform the future studies non-invasively, using the reference region method, further PET studies with arterial sampling after pre-treatment with a M4 PAM (not part of this protocol) will be needed to validate the reference region method for tracer quantification. If needed, additional methods may also be employed, to more robustly characterize the tracer kinetics in both healthy and AD subjects.
2. In Part II, intra-subject T-RT variability of the receptor availability indices will be assessed by the comparing the outcome indices of two scans obtained in the same subject ($N \geq 6$). Less than 10% T-RT variability is ideal and less than 20% T-RT variability is acceptable on average for a PET tracer.
3. In Part III, a pre-scan blood sample appropriate for determination of erythrocyte acetylcholinesterase (RBC-AChE) activity and for determination of donepezil or rivastigmine concentration (as appropriate to the AD patient enrolled) will be taken. These samples will enable correlation of the pharmacodynamic effects of the AChEI, as assessed by RBC-AChE activity, with peripheral AChEI concentrations and [^{11}C]MK-6884 binding in AD patients. Collectively, this data will inform the design of a model that can predict the effective dose range of M4 PAMs in clinical development for treatment of behavioral disturbances in AD patients.

4.2.3.2 Safety Endpoints

Systemic Safety

Safety and tolerability will be assessed throughout the study by monitoring subjects for clinical adverse experiences. Physical examinations, vital signs, 12-lead electrocardiograms (ECG) and laboratory safety tests will be performed periodically to detect any medically meaningful effects of the tracer on physiology.

Radiation Safety

This study also includes quantitative assessments of radiation exposure to the whole body and its internal organs, including the brain. In Part I, whole body PET scans will estimate [^{11}C]MK-6884 tracer radiation exposure and organ distribution (Effective Dose Equivalent, Effective Dose and radiation absorbed doses to individual organs).

4.2.3.3 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens collected for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Healthy male and female subjects (at least one of each gender) between the ages of 18 and 55 (inclusive) will be enrolled in Part I. Healthy elderly male and female subjects (at least one of each gender) between the ages of 55 and 85 years (inclusive) will be enrolled in Part II of this trial. In Part III, male and female moderate to severely impaired AD patients (MMSE score ≤ 20) between the ages of 55 and 85 years (inclusive) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

Part I, II, and III:

1. Provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research. For AD patients in Part III, if the investigator determines that the patient is unable to provide their own informed consent, the patient's legal representative must understand the study procedures and provide written informed assent for the patient, in accordance with local requirements.
2. Be male or non-pregnant and non-breast feeding female of 18 to 55 years (inclusive) (Part I) or 55 to 85 (inclusive) (Parts II and III) years of age at the pre-trial (screening) visit; further:
    a. If male and has intercourse with females of childbearing potential, subject must be willing to use a condom from the first dose of study medication until 3 months post the last dose of study medication. The use of a condom is an additional safety measure to the use of a contraceptive by the subject's partner. Female partners must additionally use one of the following methods: hormonal contraception, intra-uterine device, diaphragm, cervical cap.
    b. If female with reproductive potential: subject must demonstrate a serum β-human chorionic gonadotropin (β –hCG) level consistent with the nongravid state at the pretrial (screening) visit and agree to use (and/or have their partner use) two (2) acceptable methods of birth control beginning at the pretrial (screening) visit, throughout the trial (including washout intervals between treatment periods/panels) and until 2 weeks after the last dose of trial drug in the last treatment period. Acceptable methods of birth control are defined in Section 5.7.4.1.

c. If female of non-childbearing potential, subject/patient can be:

i. A postmenopausal female: subject/patient is without menses for at least 1 year and has a follicle stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation,

OR

ii. A female who is status post hysterectomy, oophorectomy or tubal ligation.

NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly FSH in the post-menopausal range, but tubal ligation subjects without records should be excluded. Information must be captured appropriately within the site's source documents.

3. Have a Body Mass Index (BMI) $\leq$ 35 kg/m^2, inclusive with height no greater than 195 cm and weight no greater than 136 kg. BMI = weight (kg)/height $(m)^2$.

4. Be judged to be in good health (Part I) or be generally healthy (Parts II and III) based on medical history, physical examination, vital sign measurements and ECG performed prior to randomization. Appendix 12.5 provides a table of 12-Lead Electrocardiogram Abnormality Criteria.

5. Be judged to be in good health based on laboratory safety tests (Section 7.1.3.1) obtained at the screening visit and prior to administration of the initial dose of trial drug. Section 12.6 provides an algorithm for the assessment of out-of-range laboratory values.

6. Have a negative urinary drug screen upon inclusion Exception: Subject with positive results may participate in the trial as long as the result can be rationalized as a consequence of concurrent use of a medication as permitted per protocol (see Section 5.5).

7. Be a nonsmoker and/or has not used nicotine or nicotine-containing products (e.g., nicotine patch) for at least approximately 3 months.

8. Be willing to comply with the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).

Additional Inclusion Criteria for Part II only:

9. Be willing to allow the investigator(s) to place an arterial catheter in the radial artery and is assessed via physical examination (Allen Test and/or Doppler Study) to be a good candidate for arterial catheter placement.

10. Mini Mental Status Examination (MMSE) score $\geq$ 27.

11. No history of subjective memory or other cognitive complaints

12. No objective evidence of memory or cognitive impairment

Additional Inclusion Criteria for Part III only:

13. Subjects must have moderate to severe Alzheimer's disease as defined by:

    a. Mini Mental Status Examination (MMSE) score ≤ 20

    b. Meet the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD

    c. Meet Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) criteria for AD

    d. Rosen-Modified Hachinski score ≤4

    e. MRI scan obtained at screening is consistent with a diagnosis of AD.

14. Each subject must have a clear history of cognitive and functional decline over at least one year that is either:

    a. documented in medical records, or

    b. documented by history from an informant who knows the subject well.

15. Be on a stable dose of an acetylcholinesterase inhibitor for symptomatic treatment of AD. Allowable AChEIs are donepezil and rivastigmine. Other AChEIs require prior consultation with the SPONSOR. The dose must be stable for at least the last 4 weeks before screening, and the subject must be willing to remain on the same dose for the duration of the trial. The treatment dose at screening should not be changed during the trial unless medically necessary. Additional treatments for AD that are not specified in the protocol should not be initiated during the trial. The subject and caregiver must agree that they do not plan to discontinue treatment or initiate additional AD treatments during the trial unless medically necessary. **Every effort should be made to enroll** a minimum of 3 subjects already on a stable dose of donepezil.

16. Each subject must have a reliable trial partner/caregiver (i.e., spouse, sibling, child, close friend) such that he/she is knowledgeable of the subject's condition and progress.

    a. The trial partner/caregiver must be able to understand the nature of the trial and adhere to trial requirements (e.g., visit schedules, evaluations).

    b. If appropriate, the trial partner/caregiver must be willing to accompany the subject to all visits. However, at the discretion of the investigator, the trial partner/caregiver may not be required to accompany the subject to all visits (**Note:** Trial partner/caregiver is not required to stay in-house).

c. Trial partner/caregiver must be able to provide information to study investigator/staff via telephone contact.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

Part I:

1. Is under the age of legal consent.

2. Is mentally or legally incapacitated, has significant emotional problems at the time of pretrial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder of the last 5 years. Subjects who have had situational depression may be enrolled in the trial at the discretion of the investigator.

3. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases. Subjects with a history of uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma may be enrolled in the trial at the discretion of the investigator

4. Has a history of cancer (malignancy).

   Exceptions: (1) Subjects with adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the trial; (2) Subjects with other malignancies which have been successfully treated ≥10 years prior to the pretrial (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the pretrial (screening) visit (except those cancers identified at the beginning of exclusion criterion 4); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.

5. Has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability to prescription or non-prescription drugs or food.

6. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV.

7. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.

8. Has participated in another investigational trial within 4 weeks (or 5 half-lives), whichever is greater, prior to the pretrial (screening) visit. The window will be derived from the date of the last visit in the previous trial.

9. Has QTc interval ≥ 470 msec (for males) or ≥ 480 msec (for females).

10. Is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatment periods), until the post-trial visit. There may be certain medications that are permitted, see Section 5.5.
11. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Patients that consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.
12. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day.
13. Is currently a regular or recreational user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 months.
14. Has participated in a PET study or other study involving administration of a radioactive substance or ionizing radiation within 12 months prior to the screening visit, or has undergone an extensive radiological examination within this period with a radiation burden over 10 mSv (such as a CT-scan exam or a nuclear medical examination).
15. Suffers from claustrophobia or an inability to tolerate confinement in small places and would be unable to undergo MRI or PET scanning.
16. Is any concern by the investigator regarding (1) the safe participation of the subject in the trial, (2) the ability of the subject to tolerate procedures (for example, subjects with vague low back pain syndromes or subclinical hyperactivity spectrum disorders), or (3) for any other reason the investigator considers the subject inappropriate for participation in the trial.
17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

Part II

1. Is under the age of legal consent.
2. Is mentally or legally incapacitated, has significant emotional problems at the time of pretrial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder of the last 5 years. Subjects who have had situational depression may be enrolled in the trial at the discretion of the investigator.
3. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases that is not adequately controlled through a stable medication regimen. Subjects with a history of uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma may be enrolled in the trial at the discretion of the investigator

4. Has been administered an AChEI for any purpose within the prior 3 months or anticipates a requirement for administration of an AChEI for any purpose during the course of the study investigations.
5. Has incidental findings on an MRI scan that is pathognomonic for an active disease or pathological process that requires medical intervention.
6. Has implanted or embedded metal objects, or fragments in the head or body that would present a risk during the MRI scanning procedure, or have worked with ferrous metals either as a vocation or hobby (for example, as a sheet metal worker, welder, or machinist) in such a way that might have led to unknown, indwelling metal fragments that could cause injury if they moved in response to placement in the magnetic field.
7. Has a history of cancer (malignancy).

   Exceptions: (1) Subjects with adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the trial; (2) Subjects with other malignancies which have been successfully treated ≥10 years prior to the pretrial (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the pretrial (screening) visit (except those cancers identified at the beginning of exclusion criterion 4); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.
8. Has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability to prescription or non-prescription drugs or food. **For Part II, this includes any known allergy to lidocaine which may be used as an anesthetic for the placement of the arterial catheter.**
9. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV.
10. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.
11. Has participated in another investigational trial within 4 weeks (or 5 half-lives), whichever is greater, prior to the pretrial (screening) visit. The window will be derived from the date of the last visit in the previous trial.
12. Has QTc interval ≥ 470 msec (for males) or ≥ 480 msec (for females).
13. Is unable to refrain from or anticipates the use of any prescription and non-prescription herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatment periods), until the post-trial visit. **Of note, subject should be excluded from Part II if he/she currently uses aspirin (ASA) or aspirin-containing medications (> 80 mg/day ASA), or non-steroidal anti-inflammatory drugs (NSAIDS), which cannot be discontinued 2 weeks prior to dosing and throughout the course of the study.** There are certain medications that are permitted, see Section 5.5.

14. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Patients that consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.

15. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day.

16. Is currently a regular or recreational user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 months.

17. Has participated in a PET study or other study involving administration of a radioactive substance or ionizing radiation within 12 months prior to the screening visit, or has undergone an extensive radiological examination within this period with a radiation burden over 10 mSv (such as a CT-scan exam or a nuclear medical examination).

18. Suffers from claustrophobia or an inability to tolerate confinement in small places and would be unable to undergo MRI or PET scanning.

19. Is any concern by the investigator regarding (1) the safe participation of the subject in the trial, (2) the ability of the subject to tolerate procedures (for example, subjects with vague low back pain syndromes or subclinical hyperactivity spectrum disorders), or (3) for any other reason the investigator considers the subject inappropriate for participation in the trial.

20. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

Part III:

1. Is under the age of legal consent.

2. Is mentally or legally incapacitated, has significant emotional problems at the time of pretrial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder of the last 5 years (**with the exception of AD**). Subjects who have had situational depression may be enrolled in the trial at the discretion of the investigator.

3. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases is not adequately controlled through a stable medication regimen. Subjects with a history of uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma may be enrolled in the trial at the discretion of the investigator.

4. Has been administered galantamine for any purpose within the prior 7 days or anticipates a requirement for administration of galantamine for any purpose during the course of the study investigations.

5. Has incidental findings on an MRI scan that is pathognomonic for an active disease other than AD or pathological process that requires medical intervention.

6. Has implanted or embedded metal objects, or fragments in the head or body that would present a risk during the MRI scanning procedure, or have worked with ferrous metals either as a vocation or hobby (for example, as a sheet metal worker, welder, or machinist) in such a way that might have led to unknown, indwelling metal fragments that could cause injury if they moved in response to placement in the magnetic field.

7. Has a history (within 2 years of the prestudy/screening visit) or current evidence of any neurological or neurodegenerative disorder other than AD that is associated with transient or sustained alterations in cognition.

8. Has a history (within 2 years prior to the prestudy visit) or current evidence of a psychotic disorder, or a major depressive disorder by DSM-V criteria

9. Has a history of cancer (malignancy).

   Exceptions: (1) Subjects with adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the trial; (2) Subjects with other malignancies which have been successfully treated ≥10 years prior to the pretrial (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the pretrial (screening) visit (except those cancers identified at the beginning of exclusion criterion 4); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.

10. Has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability to prescription or non-prescription drugs or food.

11. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV.

12. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.

13. Has participated in another investigational trial within 4 weeks (or 5 half-lives), whichever is greater, prior to the pretrial (screening) visit. The window will be derived from the date of the last visit in the previous trial.

14. Has QTc interval ≥ 470 msec (for males) or ≥ 480 msec (for females).

15. Is unable to refrain from or anticipates the use of any prescription and non-prescription herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatment periods), until the post-trial visit. There are certain medications that are permitted, see Section 5.5.
16. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Patients that consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.
17. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day.
18. Is currently a regular or recreational user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 months.
19. Has participated in a PET study or other study involving administration of a radioactive substance or ionizing radiation within 12 months prior to the screening visit, or has undergone an extensive radiological examination within this period with a radiation burden over 30 mSv (such as a CT-scan exam or a nuclear medical examination).
20. Suffers from claustrophobia or an inability to tolerate confinement in small places and would be unable to undergo MRI or PET scanning.
21. Is any concern by the investigator regarding (1) the safe participation of the subject in the trial, (2) the ability of the subject to tolerate procedures (for example, subjects with vague low back pain syndromes or subclinical hyperactivity spectrum disorders), or (3) for any other reason the investigator considers the subject inappropriate for participation in the trial.
22. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in

Table 2 Trial Treatments

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

[a] [^{11}C]MK-6884 doses for subjects may be adapted upwards or downwards after analysis of the actual dosimetry results of the initial subject(s) in this part of the study (see Section 7.1.5.5 for further details on adaptation of doses).

[b] [^{11}C]MK-6884 doses may be adapted upwards or downwards if indicated by the actual data found during Part I (see Section 7.1.5.5 for further details on adaptation of doses).

Trial treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the subject is allocated/assigned.

All supplies indicated in Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.2 Timing of Dose Administration

[^{11}C]MK-6884 tracer will be prepared and dosed per the instructions outlined in the site Master Batch Record.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

A sample allocation schedule is provided in Table 3.

Table 3 Sample Allocation Schedule

Study Part	Maximum Sample Size [1]	Treatment
Part I	N=6	A single IV [^{11}C]MK-6884 dose
Part II	N=10	Two separate IV [^{11}C]MK-6884 doses
Part III	N=10	A single IV [^{11}C]MK-6884 dose

[1] Sample size for Part I ranges from 3-6; sample size for Part II ranges from 6-10; and sample size for Part III ranges from 7-10.

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used within each study part in the trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

If a subject does not discontinue all prior medications within 14 days or 5 half-lives of the first dose of trial medication, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the trial.

Concurrent use of any prescription or non-prescription medication, or concurrent vaccination, during the course of the trial (i.e., after randomization or treatment allocation) must first be discussed between the investigator and Sponsor prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The subject will be allowed to continue in the trial if both the Sponsor and the investigator agree.

Parts I, II, and III: Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor.

Part II: Lidocaine will be permitted for arterial catheter placement.

In addition, the following concomitant medications/vaccinations are permitted:

1. Low dose ASA (i.e., ≤ 81 mg ASA once daily)
2. All biologics & vaccines
3. Vitamin supplements
4. Medical foods/supplement (eg, Axona®, Souvenaid®)
5. Hormone replacement therapy
6. Lipid lowering drugs
7. Erectile dysfunction treatments
8. Diabetes medications (insulin, metformin, sulfonylureas, DPP4 inhibitors, GLP-1 analogs, etc.)
9. Antihypertensives (ACE inhibitors, Angiotensin II receptor antagonists; B blockers, calcium channel blockers, direteics)
10. Analgesics/Narcotics: Current use of ≤ 2 doses/week or prior short-term use (<1 month) of more than 2 doses/week for temporary conditions is acceptable (e.g., codeine, morphine, hydromorphone, oxycodone, propoxyphene (Darvon) and its variations, & combination products that contain a narcotic).
11. Sedative/benzodiazepines: Use of the following medications is acceptable if stable for at least one month before the Screening Visit: trazodone, mirtazapine, zaleplon ≤ 5 mg, zopiclone ≤ 7.5 mg, eszopiclone ≤ 3 mg, zolpidem ≤ 5 mg, or lorazepam ≤ 1.0 mg. For other medications in this category not specified here, please contact the Sponsor for guidance.
12. Pregabalin and gabapentin: Treatment for neuropathic pain
13. Anti-inflammatory drugs such as corticosteroids: Low dose oral treatment with the equivalent of 10 mg prednisone or less, short-term (<3 weeks) oral treatment with the equivalent of 60 mg prednisone or less, if needed for management of rash, local injections into joints or bursae, topical use, inhaled or nasal use

Part III: Acetylcholinesterase inhibitors (i.e., donepezil, rivastigmine),

In addition, the following concomitant medications/vaccinations are permitted:

1. All biologics & vaccines
2. Vitamin supplements

3. Medical foods/supplement (eg, Axona®, Souvenaid®)

4. NMDA antagonists (e.g., memantine)

5. Hormone replacement therapy

6. Lipid lowering drugs

7. Erectile dysfunction treatments

8. Diabetes medications (insulin, metformin, sulfonylureas, DPP4 inhibitors, GLP-1 analogs, etc)

9. Antihypertensives (ACE inhibitors, Angiotensin II receptor antagonists; B blockers, calcium channel blockers, direteics)

10. Neuroleptics: asenapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone

11. Analgesics/Narcotics: Current use of ≤ 2 doses/week or prior short-term use (<1 month) of more than 2 doses/week for temporary conditions is acceptable (e.g., codeine, morphine , hydromorphone, oxycodone, propoxyphene (Darvon) and its variations, & combination products that contain a narcotic).

12. Sedative/benzodiazepines: Use of the following medications is acceptable if stable for at least one month before the Screening Visit: trazodone, mirtazapine, zaleplon ≤ 5 mg, zopiclone ≤ 7.5 mg, eszopiclone ≤ 3 mg, zolpidem ≤ 5 mg, or lorazepam ≤ 1.0 mg. For other medications in this category not specified here, please contact the Sponsor for guidance

13. Antidepressants: bupropion, citalopram (40 mg or less), escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine. Use of 50 mg or less at night of nortriptyline or desipramine during the trial is acceptable

14. Carbidopa/levodopa and dopamine agonists are allowed for treating restless legs syndrome

15. Pregabalin and gabapentin: Treatment for neuropathic pain

16. Anti-inflammatory drugs such as corticosteroids: Low dose oral treatment with the equivalent of 10 mg prednisone or less, short-term (<3 weeks) oral treatment with the equivalent of 60 mg prednisone or less, if needed for management of rash, local injections into joints or bursae, topical use, inhaled or nasal use

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or

the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the trial:

1. **Part II only**: currently uses aspirin or aspirin-containing medications (>80 mg/day), or non-steroidal anti-inflammatory drugs (NSAIDS), which cannot be discontinued 2 weeks prior to dosing and throughout the course of the study.

2. **Part II only**: all AChEI inhibitors

3. **Part III only**: galantamine and restrictions to dose level as noted above

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Fasting requirements for trial procedures, such as but not limited to laboratory safety evaluations are specified in Section 7.0.

Subjects will fast from all food and drinks, except water, for at least 4 hours prior to screening, predose, and poststudy laboratory safety evaluations. In Part II, subjects are allowed to have a light non-fat meal (provided by the investigator) when two tracer administrations are performed on same day.

5.7.2 Fruit Juice Restrictions

Subjects will refrain from the consumption of grapefruit juice, grapefruits and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of trial drug, throughout the trial and until the post-trial visit.

Subject also will refrain from the consumption of all fruit juices 24 hours prior to and after trial drug administration(s). All other days during the trial, consumption of fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

5.7.3 Alcohol, Caffeine, Tobacco, Activity Restrictions

5.7.3.1 Alcohol

Subjects will refrain from consumption of alcohol 24 hours prior to the pre- and post-trial visits and from 24 hours prior to and after trial drug administration(s). At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or

equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.7.3.2 Caffeine

Subjects will refrain from consumption of caffeinated beverages from 12 hours prior to the pre- and post-trial visits and from 12 hours prior to and after trial drug administration(s). At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day amounts (>6 units: 1 unit=120 mg of caffeine).

5.7.3.3 Tobacco

Smoking and/or the use of nicotine containing products is not permitted during this trial.

5.7.3.4 Activity

Subjects will avoid unaccustomed strenuous physical activity (i.e., weight lifting, running, bicycling, etc.) from the pre-trial (screening) visit until administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatments in Part II) and until the post-trial visit.

5.7.4 Contraception and Pregnancy Testing

5.7.4.1 Contraception

Women of childbearing potential can be enrolled. However, two (2) acceptable methods of barrier contraception must be used beginning at the pretrial visit, throughout the trial (including washout intervals between treatment periods/panels) and until 2 weeks after the last dose of trial drug in the last treatment period. Acceptable methods of birth control are two (2) of the following: intrauterine device (IUD-with or without local hormone release), diaphragm, spermicides, cervical cap, contraceptive sponge, and/or condoms. Abstinence is an alternative life style and subjects practicing abstinence may be included in the trial.

Alternatively, women may use an appropriate hormonal contraception instead of one of the two barrier methods. Appropriate hormonal contraception may include any marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, transdermal, intrauterine, or intramuscular agents). If hormonal contraception is used as one of the methods, hormonal contraceptives must have been used for at least 2 months prior to initial administration of trial drug for subjects to be eligible for enrollment into the trial. Subjects must be completely informed of the unknown risks of pregnancy and agree not to become pregnant during the time they are participating in this trial.

If there is any question that a subject will not be reliable in the use of appropriate contraceptive methods, they should not be entered into the trial.

Male subjects who have intercourse with females of child-bearing potential must agree to use a medically acceptable method of contraception during the trial and for 3 months after the last dose of trial drug. If their partner is pregnant: males must agree to use a condom and no

additional method of contraception is required for the pregnant partner. If their partner is of child-bearing potential: males should use a condom with spermicide. Spermicides alone are not an acceptable method of contraception. Their partner must additionally be using one of the following methods: hormonal contraception, intra-uterine device, diaphragm with spermicide, cervical cap with spermicide or female condom with spermicide. Male subject must also agree to not donate sperm during the study and for 3 months following the last dose of trial medication.

5.7.4.2 Pregnancy Testing

Female subjects of childbearing potential will be tested for serum β-human chorionic gonadotropin (hCG) at pretrial and for urine β- hCG at predose. In the case of a positive or borderline serum β-hCG pregnancy test at the pretrial visit, the subject must not enter the trial; in the case of a positive urine β-hCG pregnancy test during the trial, a serum β-hCG pregnancy test should be performed and confirmed positive. If the pregnancy has been confirmed the subject must be discontinued from the trial immediately and the pregnancy must be reported the Sponsor as outlined in Section 7.2.2.

5.7.5 Other

For potential subjects in Parts II and III (which require a baseline MRI scan), X-rays may be acquired, if indicated, as part of the screening procedures to confirm absence of indwelling metal fragments.

Investigators and designees may conduct other evaluations as medically indicated should adverse events occur or unanticipated problems arise that could have an impact on the health or wellbeing of the research volunteers. Diagnostic evaluations and treatment interventions should be rendered according to the standard of local medical care in the country in which each site is located.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through

continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.

- The subject has a positive urine drug screen at any time during the course of the trial.

5.9 Subject Replacement Strategy

If a subject discontinues from the trial, a replacement subject may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement subject will generally receive the same treatment or treatment sequence (as appropriate) as the subject being replaced. The replacement subject will be assigned a unique treatment/randomization number. The trial site should contact the Sponsor for the replacement subject's treatment/randomization number.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

A trial may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy or biologic data or other items of interest, prior to a final decision on continuation or termination of the trial. It may be necessary to keep the trial open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the trial. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. The overall trial end will then not be identified until the Sponsor has made the decision to end the trial following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be appraised of the maximum duration of the trial beyond the last subject out and the justification for keeping the trial open.

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

A primary objective of this early Phase I trial is to identify the maximum safe and well-tolerated dose and/or dosing regimen that achieve pharmacokinetic, pharmacodynamic and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that trial subjects may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this trial. This would not be defined as early termination of the trial, but rather an earlier than anticipated achievement of the trial objective(s). If a finding (e.g., pharmacokinetic, pharmacodynamic, efficacy, biologic targets, etc.) from another preclinical or clinical trial using the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial, results in the trial(s) or program being stopped for non-safety reasons, this also does not meet the definition of early trial termination.

Early trial termination is defined as a permanent discontinuation of the trial due to unanticipated concerns of safety to the trial subjects arising from clinical or preclinical trials with the trial treatment(s), comparator(s), drug(s) of the same class or methodology(ies) used in this trial.

6.0 TRIAL FLOW CHART

6.1.1 Trial Flow Chart Part I

	Screening (-4 weeks prior to Day 1)	Predose	Treatment	Post-trial [a]	Post-trial Call (at least 14 days post dose)
Administrative Procedures					
Informed Consent	X				
Informed Consent for Future Biomedical Research	X				
Review Inclusion/Exclusion Criteria	X	X			
Subject Identification Card	X				
Medical History	X				
Concomitant Medication Review	X	X	X	X	X
Clinic Procedures/Assessments					
Full Physical Examination	X	X		X	
Height	X				
Weight	X	X		X	
Vital Signs (supine heart rate, blood pressure)[b]	X	X	X	X[l]	
Vital Signs (respiratory rate, oral/tympanic body temperature)	X			X	
Orthostatic Vital Signs (heart rate, blood pressure)[b]	X	X		X[l]	
12-Lead Electrocardiogram[c]	X	X	X	X[l]	
[^{11}C]MK-6884 Administration			X[i]		
Whole Body PET/CT scan			X[j]		
Adverse Events monitoring	X	X	X	X[m]	X
Discharge from PET center[d]				X	
Follow-up Phone Call[e]				X	X

	Screening (-4 weeks prior to Day 1)	Predose	Treatment	Post-trial [a]	Post-trial Call (at least 14 days post dose)
Laboratory Procedures/Assessments					
Hematology[f]	X	X		X [l]	
Urinalysis[f]	X	X		X [l]	
Chemistry[f]	X	X		X [l]	
Serum β-Human Chorionic Gonadotropin (β-hCG) – (WOCBP Only)	X				
Serum Follicle Stimulating Hormone (FSH) – (Post-Menopausal Females Only)	X				
Urine β-Human Chorionic Gonadotropin (β-hCG) – (WOCBP Only)		X			
Urine/Blood Drug Screen –(per site SOP)	X	X [g]			
HIV/Hepatitis Screen (per site SOP)	X				
Blood for Genetic Analysis[h]		X			
Tracer Kinetics					
Venous Blood Sampling to measure the metabolite fraction in plasma			X[k]		

[a] Post-study procedures to be conducted prior to discharge (either after the scanning session, or the next day at ~ 24 hours). Some post study procedures (safety labs, ECGs, and vital signs [HR, BP] are to be performed shortly after completion of the scan; if the post study procedure is performed on the same day as the scanning session, it does not need to be repeated at the time of discharge, provided the post study procedure itself is not the reason for delaying the discharge to the next day.
[b] Obtain Pre-dose (within 4 hours prior to administration), and at approximately 5 minutes and 60 minutes post-dose, and at the end of the scanning session (~2 hours post-dose). Orthostatic vital signs will be performed following supine assessments at predose and end of scanning session only.
[c] Subjects should be resting supine for 10min prior to ECG. Obtain Pre-dose (within 4 hours prior to administration), and at approximately 5 minutes and 60 minutes post-dose, and at the end of the scanning session (~2 hours post-dose).
[d] Time of discharge may be shortly after completion of the scan (i.e., up to ~3 hours post dose), or subjects may be required to stay overnight on the day of scanning, at the discretion of the investigator and discharge the next day.
[e] Telephone interview conducted at ~24 hours post-dose (if subject was not kept overnight) and at 14 days post-dose to follow up for all adverse experiences.
[f] Laboratory safety tests (hematology, chemistry and urinalysis will be collected in the fasted state (at least 4 hours)). On treatment days, blood samples should be drawn pre-dose (up to 24 hours Pre-dose) and at the end of the scanning session.
[g] The urine/blood drug screen may be performed up to 24 hours Pre-dose.
[h] This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
[I] Time = 0. The study medication will be given as a bolus injection.
[j] PET emission scan will be initiated immediately along with the initiation of tracer injection with acquisition up to 2 hours Post-dose. A CT scan will be performed as part of the PET study to enable attenuation correction of the PET emission scan. The CT scan may be performed before or after the PET scan.
[k] Venous blood samples for measuring metabolites in plasma will be collected at the following time points: 5, 15, 30, 45, 60 and 90, minutes post-dose. After each sample, the line will be flushed with saline. The time points and/or number of samples may be adjusted as necessary. Additional blood samples may be taken if necessary, adhering to maximum blood volume limits (see appendix Section 12.4). The clinical site SOP will be followed for collection and analysis of plasma samples.
[l] Shortly after scan completion
[m] Assessment for potential adverse experiences should be conducted at ~ 24 post dose either by phone or in the clinic.

6.1.2 Trial Flow Chart Part II

	Screening (-4 weeks prior to Day 1)	Predose[q]	Treatment	Post-trial[a]	Post-trial Call (at least 14 days post last dose)
Administrative Procedures					
Informed Consent	X				
Informed Consent for Future Biomedical Research	X				
Inclusion/Exclusion Criteria	X	X			
Subject Identification Card	X				
Medical History	X				
Concomitant Medication Review	X	X	X	X	X
Clinic Procedures/Assessments					
Allen Test or Doppler Study (for radial artery assessment) [b]	X				
Mini Mental Status Examination (MMSE)	X				
Full Physical Examination	X	X		X	
Height	X				
Weight	X	X		X	
Vital Signs (supine heart rate, blood pressure)[c]	X	X	X[c]	X[o]	
Vital Signs (respiratory rate, oral/tympanic body temperature)	X			X	
Orthostatic Vital Signs (heart rate, blood pressure) [c]	X	X	X	X[o]	
12-Lead Electrocardiogram[d]	X	X	X	X[o]	
Brain MRI[e]	X				
[^{11}C]MK-6884 Administration			X[k]		
Brain PET/CT Scan			X[l]		
Adverse Events monitoring	X	X	X	X [p]	X

	Screening (-4 weeks prior to Day 1)	Predose[q]	Treatment	Post-trial[a]	Post-trial Call (at least 14 days post last dose)
Discharge from PET center[f]				X	
Follow-up Phone Call[g]				X	X
Laboratory Procedures/Assessments					
Hematology[h]	X	X		X [o]	
Urinalysis[h]	X	X		X [o]	
Chemistry[h]	X	X		X [o]	
Serum β-Human Chorionic Gonadotropin (β-hCG) (If applicable)	X				
Serum Follicle Stimulating Hormone (FSH) – (Post-Menopausal Females Only)	X				
Urine β-Human Chorionic Gonadotropin (β-hCG) – (WOCBP Only)		X			
Urine/Blood Drug Screen –(per site SOP)	X	X [i]			
HIV/Hepatitis Screen (per site SOP)	X				
Blood for Genetic Analysis[j]		X			
Tracer Kinetics					
Arterial Blood Sampling (for tracer metabolism-counts and metabolites)[r]			X[m]		
Arterial Blood sampling (for radioactivity in whole blood and plasma)[r]			X[n]		

[a] Post-study procedures to be conducted prior to discharge (either after the scanning session, or the next day at ~ 24 hours). Some of the post study procedures (safety labs, ECGs, and vital signs [HR, BP]) should be done shortly after completion of the scan; if the post study procedure is done on the same day as the scanning session, it does not need to be repeated at the time of discharge, provided the post study procedure itself is not the reason for delaying the discharge to the next day.

[b] Assessment of the radial artery will be performed via the Allen Test first. The Doppler Study may be conducted if the Allen Test appears abnormal and at the discretion of the Investigator.

[c] Obtain Pre-dose (within 4 hours prior to administration), and at approximately 5 minutes and 60 minutes post-dose, and at the end of each scanning session (~2 hours post-dose). Orthostatic vital signs will be performed following supine assessments at predose and end of each scanning session only. The predose assessments for the second scan may be omitted if the scans are performed on the same day.

[d] Subjects should be resting supine for 10min prior to ECG. Obtain Pre-dose (within 4 hours prior to administration), and at approximately 5 minutes and 60 minutes post-dose, and at the end of each scanning session (~2 hours post-dose). If both scans are done at the same day, the pre-dose ECG will only be performed prior to the first scan.

[e] MRI to be performed after all other screening assessments of screening 1 are found acceptable. A separate screening visit may be scheduled for the MRI as needed. In case of technical problems, the MRI scan may be repeated.

[f] Time of discharge may be shortly after completion of the scan (i.e. up to ~3 hours post dose), or subjects may be required to stay overnight on the day of scanning, at the discretion of the investigator and discharge the next day.

[g] Telephone interview conducted at ~24 post last dose (if subject is not kept overnight) and at 14 days post-dose (after second IV dose) to follow up for all adverse experiences.

[h] Laboratory safety tests (hematology, chemistry and urinalysis) will be collected in the fasted state (at least 4 hours) . PT/aPTT will be measured at screening. On scan days, blood samples should be drawn before the first dose (up to 24 hours Pre-dose) and at the end of the second scan (prior to discharge). If the 2 scans are done on separate non-consecutive days, blood samples should be drawn each day prior to dosing (within 24 hours Pre-dose) and at the end of each scan. If the 2 scans are done on consecutive days, blood samples should be drawn prior to the first scan and at the end of the second scan (total 2 blood draws).

[i] The urine/blood drug screen may be performed within 24 hours prior to dosing.

[j] This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

[k] Two bolus injections of [^{11}C]MK-6884 will be given with a minimum interval of 3 hr. Time = 0 relative to each injection.

[l] PET emission scan will be initiated immediately along with the initiation of each tracer injection with acquisition up to ~90 minutes post-dose. A CT scan will be performed as part of the PET study to enable attenuation correction of the PET emission scan. The CT scan may be performed before or after the PET scan. (Scanning duration time may be adjusted based on data from Part I and initial data from Part II).

[m] Arterial blood samples will be collected for metabolite measurements at approximately 5, 15, 30, 45, 60 and 90minutes post-dose for each scan. After each sample, the line will be flushed. The time points and/or number of samples taken may be adjusted as necessary, adhering to the maximum blood volume limits (See Appendix 12.4). The clinical site SOP will be followed for collection and analysis of blood samples.

[n] Arterial blood samples will be collected for radioactivity in whole blood and plasma. For each scan, arterial samples will be taken at approximately 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120 and 150 seconds, and 3, 5, 15, 30, 45, 60, 75, and 90 minutes post-dose. The time points and/or number of samples taken may be adjusted as necessary, adhering to maximum blood volume limits (See Appendix 12.4) The clinical site SOP will be followed for collection and analysis of blood samples.

[o] Shortly after scan completion

[p] Assessment for potential adverse experiences should be conducted at ~ 24 post dose either by phone or in the clinic.

[q] Pre-dose procedures to be performed only prior to the first scan if both scans are done at the same day.

[r] Arterial blood sampling may not be performed based on data from the initial group of subjects (at least N=3).

6.1.3 Trial Flow Chart Part III

	Screening (-4 weeks prior to Day 1)	Predose	Treatment	Post-trial[a]	Post-trial Call (at least 14 days post last dose)
Administrative Procedures					
Informed Consent/Assent	X				
Informed Consent/Assent for Future Biomedical Research	X				
Review Inclusion/Exclusion Criteria	X	X			
Subject Identification Card	X				
Medical History	X				
Concomitant Medication Review	X	X	X	X	X
Clinic Procedures/Assessments					
Mini Mental Status Examination (MMSE)	X				
Rosen-Modified Hachinski Scoring	X				
Full Physical Examination	X	X		X	
Height	X				
Weight	X	X		X	
Vital Signs (supine heart rate,blood pressure) [b]	X	X	X	X[l]	
Vital Signs (respiratory rate, oral/tympanic body temperature)	X			X	
Orthostatic Vital Signs (heart rate, blood pressure)[b]	X	X		X[l]	
12-Lead Electrocardiogram [c]	X	X	X	X[l]	
Brain MRI [d]	X				
[^{11}C] MK-6884 Administration			X [j]		
Brain PET/CT scan			X [k]		
Adverse Events monitoring	X	X	X	X [m]	X
Discharge from PET center [e]				X	

	Screening (-4 weeks prior to Day 1)	Predose	Treatment	Post-trial[a]	Post-trial Call (at least 14 days post last dose)
Follow-up Phone Call [f]				X	X
Laboratory Procedures/Assessments					
Hematology [g]	X	X		X[l]	
Urinalysis [g]	X	X		X[l]	
Chemistry [g]	X	X		X[l]	
Serum β-Human Chorionic Gonadotropin (β-hCG) (if applicable)	X				
Serum Follicle Stimulating Hormone (FSH) – (Post-Menopausal Females Only)	X				
Urine β-Human Chorionic Gonadotropin (β-hCG) – (WOCBP Only)		X			
Urine/Blood Drug Screen –(per site SOP)	X				
HIV/Hepatitis Screen (per site SOP)	X				
Blood for Genetic Analysis [i]		X			
Pharmacokinetic/Pharmacodynamic Evaluations					
Blood Sample for Plasma Donepezil or Rivastigmine [n]		X			
Blood Sample for RBC-AChE Activity [n]		X			

[a] Post-study procedures to be conducted prior to discharge (either after the scanning session, or the next day at ~ 24 hours). Some of the post study procedures (safety labs, ECGs, and vital signs [HR, BP]) should be done shortly after completion of the scan; if the post study procedure is done on the same day as the scanning session, it does not need to be repeated at the time of discharge, provided the post study procedure itself is not the reason for delaying the discharge to the next day.

[b] Obtain Pre-dose (within 4 hours prior to administration), and at approximately 5 minutes and 60 minutes post-dose, and at the end of the scanning session (~90 minutes post-dose). Orthostatic vital signs will be performed following supine assessments at predose and end of scanning session only.

[c] Subjects should be resting supine for 10min prior to ECG. Obtain Pre-dose (within 4 hours prior to administration), and at approximately 5 minutes and 60 minutes post-dose, and at the end of the scanning session (~90 minutes post-dose).

[d] MRI to be performed after all other screening assessments of screening 1 are found acceptable. A separate screening visit may be scheduled for the MRI as needed. In case of technical problems, the MRI scan may be repeated.

[e] Time of discharge may be shortly after completion of the scan (i.e. up to ~3 hours post dose), or subjects may be required to stay overnight on the day of scanning, at the discretion of the investigator and discharge the next day.

[f] Telephone interview conducted at ~24 ours post-dose (if patient is not kept overnight) and at 14 days post-dose to follow up for all adverse experiences.

[g] Laboratory safety tests (hematology, chemistry and urinalysis will be collected in the fasted state (at least 4 hours). On treatment days, blood samples should be drawn pre-dose (up to 24 hours Pre-dose) and at the end of the scanning session.

[i] This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

[j] Time = 0. The study medication will be given as a bolus injection.

[k] PET emission scan will be initiated immediately along with the initiation of tracer injection with acquisition up to ~ 90 minutes post-dose. A CT scan will be performed as part of the PET study to enable attenuation correction of the PET emission scan. The CT scan may be performed before or after the PET scan. (Scanning duration time may be shortened to approximately 60 minutes based on data from Part II),

[l] Shortly after scan completion.

[m] Assessment for potential adverse experiences should be conducted at ~ 24 post dose either by phone or in the clinic.

[n] Venous blood samples will be collected no more than 90 minutes before administration of study drug [^{11}C] MK-6884. One sample will be collected for either donepezil or rivastigmine (depending on the subject's concomitant medication). Refer to the Operations Manual for collection, preparation, storage and shipment of plasma samples.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject/patient within 14 days before starting the trial.

For AD subjects enrolled on a stable dose of an acetylcholinesterase inhibitor (donepezil or rivastigmine), the dose and dose schedule of their AChEI medication will be used for pharmacokinetic (PK)_and pharmacodynamics (PD) evaluations in conjunction with the blood assays. The site staff will record the time when the last dose of AChEI was taken prior to blood sampling for the PK and PD assays.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Administration of trial medication will be witnessed by the investigator and/or trial staff.

7.1.2 Clinical Procedures/Assessments

Physical Exam

The physical exam assessments will be defined and conducted per the site SOP.

Allen Test or Doppler Study (Part II)

This will be done at Screening for Part II subjects only in order to assess the radial artery for blood sampling.

Body Weight and Height

Body weight and height will be obtained with the subjects shoes off, jacket or coat removed.

Body Mass Index (BMI)

BMI equals a person's weight in kilograms divided by height in meters squared. (BMI=kg/m2). Body weight and height will be obtained with the subjects shoes off, jacket or coat removed. BMI can be rounded to the nearest whole number.

12-Lead ECG

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Subjects may need to be shaved to ensure proper lead placement.

Subjects should be resting in the supine position for at least 10 minutes prior to each ECG measurement. Subject position during ECG collection (e.g., supine) should be consistent throughout the study.

The correction formula to be used for QTc is Fredericia.

If repeat ECGs are required the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker pen to ensure reproducible electrode placement.

Body Temperature

Body temperature will be measured with an oral or tympanic thermometer. The same method (e.g. oral or tympanic) must be used for all measurements for each individual subject and should be the same for all subjects.

Vital Sign Measurements (Heart Rate and Blood Pressure)

Subjects should be resting in a supine position for at least 10 minutes prior to having vital sign measurements obtained. Supine vital signs will include heart rate (HR) and blood pressure (BP). The correct size of the blood pressure cuff and the correct positioning on the subjects' arm is essential to increase the accuracy of blood pressure measurements. The same method (e.g., manual or automated) must be used for all measurements for each individualsubject and should be same for all subjects.

Orthostatic vital signs (HR and BP) will also be obtained. Subjects should be resting in a supine position for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic vital signs.

Imaging Procedures

Whole Body (WB) PET/CT Scan (Part I)

In Part I only, WB PET imaging will be performed according to the clinical site SOP on a PET/CT camera. Whole-body CT transmission scan will be obtained for attenuation correction before or after the emission PET scan. Following [^{11}C]MK-6884 administration, a series of whole body PET images will be obtained according to the clinical site SOP. The acquisition will be conducted over about ~2 hours. The acquisition duration may be shortened at the discretion of the investigator.

Magnetic Resonance Imaging (MRI) (Parts II and III)

In Parts II and III only, a MRI scan of the brain will be obtained per the clinic SOPs to enable regions of interest (ROIs) delineation. The MRI visit may take place at any time during the screening period after all other screening assessments from the Screening 1 visit are deemed acceptable. The MRI may be waived at the discretion of the investigator if the subject/patient has had a previous MRI performed within the past year at the same local imaging center where the current study is being conducted.

Brain PET/CT Scan (Parts II and III)

In Parts II and III only, the brain scans will be performed according to the clinical site SOPs on a PET/CT or PET camera. For each scanning session, subjects will be positioned on the scanner bed with the head within the center of axial and transaxial field of view. The head will be restrained to reduce movement artifacts during the scan. A transmission scan of the brain will be obtained either before or after the PET scan to enable attenuation correction of the emission scan. [^{11}C]MK-6884 will be administered by IV injection while the subject is lying supine on the imaging table. The brain PET scan will be initiated along with the initiation of tracer injection. Serial dynamic imaging frames will be obtained up to a total duration of approximately 90 minutes for each session according to clinical site SOPs. The acquisition duration may be shortened at the discretion of the investigator.

Part III Only: every effort should be made to get a full dynamic scan for 90 minutes (if required based on available data from the ongoing trial). If an AD subject is unable to tolerate the full duration of 90 minutes, as determined by the investigator, or an unexpected intolerance event occurs at or after 60 minutes into a full scan, the scan can be concluded at or after 60 minutes. PET data for such a shortened scan should be reconstructed following the same protocol as a normal scan, without inclusion of the truncated time frames.

Venous (Parts I and III) and Arterial (Part II) Blood Sampling

Intravenous (IV) and radial arterial catheters will be placed in Part I and Part II subjects, respectively, for blood sampling. In Part III, venous blood samples will be drawn from AD subjects as outlined in Section 6.1.3 Trial Flow Chart. The number of blood samples may be changed, if necessary, adhering to maximum blood volume limits (See Appendix 12.4). The clinical site SOP will be followed for collection and analysis of blood samples.

Part II Only: no more than 2 arterial lines, preferably in different hands, may be placed in any one subject over the course of the entire study.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 4.

Table 4 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-Human Chorionic Gonadotropin (β-hCG) (If applicable)
Hemoglobin	Alkaline phosphatase	Glucose	Urine β-Human Chorionic Gonadotropin (β-hCG) (If applicable)
Platelet count	Alanine aminotransferase (ALT)	Protein	Follicle Stimulating Hormone (FSH) (if applicable)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Hepatitis
PT/aPTT (Part II screening only)	Bicarbonate	Microscopic exam, if abnormal results are noted	HIV
	Calcium		Urine/Blood Drug Screen (per site SOP)
	Chloride		
	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Urea/Blood Urea Nitrogen (BUN)		

In each Part, subjects will fast from all food and drink except water for at least 4 h prior to screening, pre-dose and post-trial laboratory safety evaluations.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

Quantification of tracer in plasma will be performed to obtain the input function for PET tracer kinetic modeling. In addition, the decision as to which Part III samples collected will be assayed for exploratory evaluations will be collaboratively determined by the appropriate departments within the Sponsor's organization.

7.1.3.2.1 Blood Collection for [^{11}C]MK-6884 Tracer Kinetics (Parts I and II)

Prior to dosing, IV catheter will be placed for Part I subjects and radial arterial catheters will be placed for Part II subjects for arterial blood sampling. The clinical site SOP will be followed for collection and analysis of blood samples. Samples will be collected and analyzed on site.

7.1.3.2.2 Blood Collection for Plasma Donepezil or Rivastigmine (Part III)

Blood sample for determination of plasma donepezil or rivastigmine levels should be taken no more than 90 minutes prior to [^{11}C]MK-6884 administration. Sample collection, storage and shipment instructions for plasma samples will be provided in the Operations Manual.

7.1.3.2.3 Blood Collection for Plasma AChE Activity (Part III)

Blood samples for determination of erythrocyte acetylcholinesterase (RBC-AChE) activity should be taken no more than 90 minutes prior to [^{11}C]MK-6884 administration. Sample collection, storage and shipment instructions for plasma samples will be provided in the Operations Manual.

7.1.3.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the appendix Section 12.2

7.1.3.4 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

Leftover DNA for future research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

The investigator or trial coordinator must notify the Sponsor when a subject has been discontinued/withdrawn from the trial. If a subject discontinues for any reason at any time during the course of the trial, the subject may be asked to return to the clinic (or be contacted) for a post-trial visit (approximately 14 days after the last dose of trial drug is given) to have the applicable procedures conducted. However, the investigator may decide to perform the post-trial procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-trial visit occurs prior to 14 days after the last dose of trial drug is given , the investigator should perform a follow-up phone call 14 days after the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Domiciling

Parts I and III: Subjects will report to the research center on Day -1 (Part I) or on Day 1 (Part III) and will be discharged after completion of all post-dose study procedures following the scanning session on Day 1. At the discretion of the investigator, subjects may be

requested to stay longer or return to the unit in the event of a technical failure that prevents tracer administration or scanning.

Part II: Subjects will report to the research center on Day -1 and will be discharged after completion of all post-dose study procedures following Scan 1 and Scan 2. At the discretion of the investigator, subjects may be requested to stay longer or return to the unit in the event of a technical failure that prevents tracer administration or scanning.

7.1.4.4 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

MRI/PET/CT Scanners and related imaging equipment, equipment for measuring blood pressure, ECG machine, HPLC system, Gamma Counter, Centrifuge.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening (Part I, Part II and Part III)

Within approximately 4 weeks prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1.

Screening procedures may be repeated after consultation with the Sponsor. In Parts II and III, a baseline MRI scan of the brain will be obtained for region-of-interest (ROI) delineation and to make sure the MRI scan is consistent with a diagnosis of AD (Part III only).

7.1.5.2 Treatment Period (Part I, Part II, and Part III)

In Parts I, II, and III, dosing and study procedures may be conducted any time during the day as the PET scan outcome measures are relatively resistant to the impact of diurnal variations in physiology.

Part I

<u>Pre-dose</u>

An IV catheter will be placed for injection of the radiotracer and venous blood sampling.

Dosing/Scanning

A single, open-label dose of ≤ 4.9 µg [^{11}C]MK-6884 with a radiation dose ~370 MBq will be administered by IV injection through an indwelling venous catheter while the subject is lying supine on the imaging table. Immediately following the [^{11}C]MK-6884 administration, a series of whole body PET images will be obtained over a period of up to approximately 120 minutes. CT scans will be obtained at each bed position, for attenuation correction.

The sequence of procedures that should be followed in Part I (refer to Study Flowchart in Section 6.0) is outlined in Table 5.

Table 5 Part I Procedures

Time Period	Description
-90 to -10 minutes	-All procedures requiring needle sticks will be completed, including antecubital venous lines. -Subjects should be asked to micturate immediately prior to the next time period.
Approximately 30 minutes pre-dose	-Subjects will rest supine on the imaging table while baseline vital signs and ECGs are obtained per the study flowchart (Section 6.0). -Venous blood sample will be drawn before tracer administration for baseline laboratory safety evaluations (up to 24 hours prior). -A whole body CT scan is obtained (the time of the CT scan can be at the discretion of the investigator, target within 5 min before acquisition)
Time "0"	[^{11}C]MK-6884 administration, PET scan initiated
0 to ~ 120 minutes	Subjects will be asked to remain motionless on the imaging table while the scans are acquired. -HR, BP, and 12-lead ECGs will be obtained during this time period per the study flowchart (Section 6.0) -Venous blood samples will be collected for measurement of radioactivity associated with the parent tracer and its metabolites (Section 6.0)
End of scanning sessions	HR, BP, EGG and blood for laboratory safety evaluations will be collected per the study flowchart (Section 6.0). Indwelling venous catheter will be removed.

All images will be acquired using the HI-Rez Biography PET/CT scanner. First, a CT scout will be acquired to set the axial field of view (FOV). The axial FOV should extend from the top of the head to the middle of the thighs (~ 8 bed positions). Then, a low current CT will be acquired for both PET attenuation correction and anatomical information. Following the CT 3D PET images will be acquired sequentially for an overall study duration of approximately 2 hours.

WB 1-3: 30s/bed (~4 min per WB)

WB 4-6: 60s/bed (~8 min per WB)

WB 7-8: 120s/bed (~16 min per WB)

WB 9: 240s/bed (~32 min per WB)

After this sequence of PET acquisitions, the subject will be moved out of the camera and will be encouraged to void their urine. The actual times of scanning and the acquisition sequence may be varied by the investigator, as indicated by the data that emerges during the course of the study – See Section 7.1.5.5. In order to use the whole body PET images for dosimetry calculations, the dose calibrator and PET scanner will be cross-calibrated.

Catheters will be removed after all of the procedures requiring venous access have been completed.

Postdose

Subjects may stay overnight at the discretion of the investigator.

Part II

Pre-dose

Prior to administration of [^{11}C]MK-6884, a trained staff member will place an arterial catheter in a radial artery for the collection of blood samples. A topical anesthetic may be used to reduce some of the discomfort associated with insertion of the catheter. The staff member placing the line may also inject a small amount of lidocaine subcutaneously to further reduce any discomfort when the actual catheter is placed. The IV catheter for tracer injection will be placed contralateral to the radial arterial catheter and the IV catheter for arterial blood sampling.

Dosing/Scanning

A low-dose CT scan of the brain will be performed to enable attenuation correction of the emission scan. Separate single, open-label doses of [^{11}C]MK-6884 will be administered by IV injection through an indwelling venous catheter while the subject is lying supine on the imaging table (dose may be adapted based on the data from Part I). The brain PET scan will be initiated along with the initiation of the tracer injection. The sequence of procedures that should be followed in Part II (refer to Study Flowchart in Section 6.0) is outlined in Table 6.

Table 6 Part II Procedures

Time Period	Description
-90 to -10 minutes	-All procedures requiring needle sticks will be completed, including antecubital venous and arterial lines. -Subjects should be asked to micturate immediately prior to the next time period.
Approximately 30 minutes pre-dose	-Subjects will rest supine on the imaging table while baseline vital signs and ECGs are obtained per the study flowchart (Section 6.0). -Venous blood samples will be drawn before tracer administration for baseline laboratory safety evaluations (up to 24 hours prior). *This is done prior to the first dose only if both doses are done on the same day or if both doses are done on consecutive days. If the second dose is done on a different non-consecutive day, blood samples should be obtained for baseline laboratory safety evaluations prior to the second scan as well.* -A brain attenuation CT scan is obtained (the time of the CT scan can be at the discretion of the investigator)
Time "0"	[^{11}C]MK-6884 administration[1], PET scan initiated
0 - ~90 min	-Subjects will be asked to remain motionless on the imaging table while the scans are acquired. -HR, BP, and 12-lead ECGs will be obtained during this time period per the study flowchart (Section 6.0) -Arterial blood samples will be collected for tracer metabolism counts per the study flowchart (Section 6.0) - Arterial blood samples will be collected for radioactivity counts per the study flow chart (Section 6.0).
End of scanning session	- HR, BP, and ECG will be collected per the study flow chart (Section 6.0). Indwelling catheter will be removed. -Venous blood samples will be drawn for laboratory safety evaluations. *This is done at the end of the second scan only if both doses/scans are done on the same day or if both doses/scans are done on consecutive days. If the second scan is done on a different non-consecutive day, blood samples should be obtained at the end of the first scan as well for laboratory safety evaluations.*

[1] Sequence procedures for the second dose (to be administered at least 3 hours after the first dose) will follow the time frame as for the first dose. If second dose/scanning session occurs on a different day due to difficulties performing both scans in one day, then all procedures starting from row 1 of this table will be followed.

A brain PET scan will be initiated immediately following each dosing. For each scanning session, subjects will be positioned on the scanner bed with the head within the center of axial and transaxial fields of view. The head will be restrained to reduce movement artifacts during the scan. Baseline sensory conditions (dimmed room lighting, reduced noise) will be imposed and maintained throughout the session.

Catheters will be removed after all of the procedures requiring arterial and venous access have been completed.

Postdose

Subjects may stay overnight after the day of scanning at the discretion of the investigator.

Part III

Pre-dose

An IV catheter will be placed for injection of the radiotracer.

Dosing/Scanning

In Part III, a single IV dose of approximately 370 MBq (10 mCi, ≤ 4.9 μg) [^{11}C]MK-6884 will be administered. A single brain scan will be performed after the dose, and positron emission images of the brain will be obtained for approximately 90 minutes after the administration of [^{11}C]MK-6884 to verify the BP_{ND} of the [^{11}C]MK-6884 ligand.

The sequence of procedures that should be followed in Part III (refer to Study Flowchart in Section 6.0) is outlined in Table 7.

Table 7 Part III Procedures.

Time	Description
Approximately 2 hours to 90 minutes pre-dose	-Venous blood sample will be drawn before tracer administration for baseline laboratory safety evaluations.
-90 to -10 minutes	-Note all procedures requiring needle sticks (including antecubital venous lines) will be completed -Venous bloods sample will be drawn for evaluation of plasma donepezil/rivastigmine level and RBC-AChE activity during this period. -Subjects should be asked to micturate immediately prior to the next time period.
Approximately 30 minutes pre-dose	-Subjects will rest supine on the imaging table while baseline vital signs and ECGs are obtained per the study flowchart (Section 6.0). -A brain attenuation CT scan is obtained (the time of the CT scan can be at the discretion of the investigator) [1]
Time "0"	[^{11}C]MK-6884 administration, PET/CT scan initiated

Time	Description
0 to ~ 90 minutes	Subjects will be asked to remain motionless on the imaging table while the scans are acquired.[1] -HR, BP, and 12-lead ECGs will be obtained during this time period per the study flowchart (Section 6.0)
End of scanning sessions	HR, BP, ECG and blood for laboratory safety evaluations will be collected per the study flowchart (Section 6.0). Indwelling venous catheter will be removed.

[1] Every effort should be made to get a full dynamic scan for 90 minutes (if required based on available data from the ongoing trial). If an AD subject cannot tolerate the full duration of 90 minutes, as determined by the investigator, or, an unexpected intolerance event occurs at or after 60 minutes into a full scan, the scan can be concluded at or after 60 minutes. PET data for such a shortened scan should be reconstructed following the same protocol as a normal scan, without inclusion of the truncated time frames.

A brain PET scan will be initiated immediately following dosing. For the scanning session, subjects will be positioned on the scanner bed with the head within the center of axial and transaxial fields of view. The head will be restrained to reduce movement artifacts during the scan. Baseline sensory conditions (dimmed room lighting, reduced noise) will be imposed and maintained throughout the session.

Catheters will be removed after all of the procedures requiring venous access have been completed.

Postdose

Subjects may stay overnight at the discretion of the investigator.

7.1.5.3 Post-Trial

Post-study procedures will be performed either shortly after the last scanning session, or just prior to discharge which may be at ~ 24 hours post final dose (if the subject is kept overnight at the investigator's discretion) (see the Study Flowchart in Section 6.0). Assessment for potential adverse experiences will be conducted at ~24 hours post dose either by phone or at the clinic, followed by an additional phone call conducted at 14 days post final dose.

7.1.5.4 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the blood sample collections for [^{11}C]MK-6884/tracer kinetics (in Parts I and II) and the PET scans (in Parts I, II, and III) are the critical procedures.

At any postdose time point, the blood sampling for tracer kinetics and PET scans need to be performed as close to the exact time point as possible. When multiple procedures are scheduled for the same time, the collection of venous (Part I) or arterial (Part II) blood samples will have the highest priority. All other procedures should be completed as close to the prescribed/scheduled time as possible. Trial procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the trial with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

7.1.5.5 Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters

This is a Phase I assessment of MK-6884 in humans, and the pharmacokinetic, pharmacodynamic and safety profiles of the compound is still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Modifications to the dose, dosing regimen and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

As such, some alterations from the currently outlined radiation dose and/or dosing regimen may be permitted based on newly available data, but the tracer mass dose as well as yearly effective dose may not exceed those limits currently outlined in the protocol. Specifically, any upward titration in the radiation dose for Parts II and III may occur if needed based on Part I data as long as it remains below the yearly acceptable limits of radiation exposure.

- Repeat of or adjustment in the dose of the trial drug administered in any given period/panel
- Omission of one part of the study or a dose within Part II
- Adjustment of the dosing interval (Part II)
- Instructions to take trial drug with or without food or drink may also be modified based on newly available data
- Changes to the time interval between dosing and PET scans
- Changes to the scanning protocol
- Changes to tracer kinetics sampling timepoints

If it is determined that incomplete or aberrant data has been captured during the PET measurements at any post-randomization trial visit, the subject may be asked to repeat the treatment/scan. The evaluation to determine whether the treatment/scan is to be repeated will be done on an individual basis per subject, and the decision will be reached by mutual agreement of the Sponsor and investigator. Up to two (2) treatment/scan per subject may be repeated. Repeating treatment/scan may result in an increase of the subject's cumulative exposure and/or may increase the total blood volume with approximately 50 mL per repeat in Part I, approximately 90 mL in Part II, and approximately 33 mL in Part III. The resulting exposure or blood volume increases will be deemed acceptable by the Sponsor and investigator for that subject. The total blood volume collected should remain <500 mL. A subject may be discontinued from the trial and be replaced at the investigator’s discretion after one failed repeat treatment/scan.

The blood sampling scheme for tracer kinetics currently outlined in the protocol may be modified during the trial based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, pharmacokinetic, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial (Section 12.4).

The timing of procedures for assessment of safety procedures (e.g., vital signs, ECG, safety laboratory tests, etc.) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, pharmacokinetic or pharmacodynamic data (e.g., to obtain data closer to the time of peak plasma concentrations). Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (e.g., adding creatinine kinase to serum chemistry panel that was already drawn. These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the Sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/ERC at the discretion of the investigator.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

For randomized subjects only, all adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by investigator if they are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

The subject has taken (accidentally or intentionally) any drug administered as part of the protocol and exceeding the dose as prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

The targeted radiation doses of [11C]MK-6884 are specified in the protocol. The actual radiation dose administered will be as specified per protocol, with a deviation of up to 10% greater than prescribed deemed acceptable, per local standards.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 8 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse

event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 8. The investigator's assessment of causality is required for each adverse event. Refer to Table 8 for instructions in evaluating adverse events.

Table 8 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Clinical Pharmacology Statistics Department in collaboration with the Pharmacology Imaging and Clinical Pharmacology Departments of the Sponsor.

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

Statistical Methods

Safety (All Parts)

Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for subjects, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back- transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

Primary (Pharmacodynamics; Parts I, II, and III)

Whole body and internal organ radiation dose will be evaluated by whole body PET scans (Part I). Efficacy measurements to investigate M4 PAM receptor availability and its inter-subject variability in healthy subjects (Part II) will be evaluated via two administrations of [^{11}C]MK-6884 and brain PET scanning and will include: (1) volume of distribution, or one of its surrogate (2) test-retest variability of volume of distribution, or one of its surrogate. Efficacy measurements to investigate M4 PAM receptor availability and its inter-subject variability in AD patients (Part III) will be evaluated via single administration of [^{11}C]MK-6884 and brain PET scanning and will include: (1) binding potential, or one of its surrogate.

Power

Up to 26 (N=3-6 in Part I, N=6-10 in Part II, and N=7-10 in Part III) subjects will be included in the study. Given the investigational nature of this study no sample size calculation has been performed.

8.2 Statistical Analysis Plan

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Pharmacology Imaging and Translational Medicine Departments of the Sponsor.

The analysis of the data obtained in Part I of this study will be the responsibility of the Leuven PET center. The analysis of the data obtained in Part II and Part III of the study will be the responsibility of the Merck Translational Imaging Biomarkers Department.

If, after the study has begun, changes are made to the statistical and image analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report (CSR).

8.2.1 Hypotheses

Part I

Primary

1. Dosimetry calculations based on Part 1 data will support multiple [^{11}C]MK-6884 injections in humans.

Part II

Primary

1. The average intra-subject T-RT variability of M4 receptor density index measured from [^{11}C]MK-6884 PET data is acceptable ($\leq$ 20%).

8.2.2 Analysis Endpoints

Primary (Safety)

Safety and tolerability will be assessed throughout the study by monitoring subjects for clinical adverse experiences. Physical examinations, vital signs, 12-lead electrocardiograms (ECG) and laboratory safety tests will be performed periodically to detect any medically meaningful effects of the tracer on physiology.

Primary (Pharmacodynamics)

Whole body and internal organ radiation dose will be evaluated by whole body PET scans (Part I). Efficacy measurements to investigate M4 PAM receptor availability and its inter-subject variability in healthy subjects (Part II) will be evaluated via two administrations of [^{11}C]MK-6884 and brain PET scanning and will include: (1) volume of distribution, or one of its surrogate (2) test-retest variability of volume of distribution, or one of its surrogate. Efficacy measurements to investigate M4 PAM receptor availability and its inter-subject

variability in AD patients (Part III) will be evaluated via single administration of [^{11}C]MK-6884 and brain PET scanning and will include: (1) binding potential, or one of its surrogate.

8.2.3 Approaches to Analyses

The following populations are defined for the analysis and reporting of data. All subjects will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Subjects as Treated (AST) - All subjects who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP) – The set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations. Major protocol deviations will be identified to the extent by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the primary analysis dataset. This population will be used for assessments of pharmacodynamics.

8.2.4 Statistical Methods

Safety (All Parts)

Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for subjects, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back- transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

Pharmacodynamics

Part I

The whole body and internal organ radiation burden associated with a single IV dose of [^{11}C]MK-6884 (~ 370 MBq, $\leq$ 4.9 μg) administered to healthy subjects will be estimated using methods from the site. The primary measure of radiation safety will be the Effective Dose (ED), a weighted composite measure of the radiation absorbed doses in multiple compartments.

Part II

Brain extraction and grey and white matter segmentation will be performed in each subject's MRI scan. A human brain atlas will be aligned to the extracted subject MRI brain via a non-linear registration algorithm.

[^{11}C]MK-6884 dynamic PET images will be corrected for decay, scatter, random coincidences, photon attenuation and motion (frame to frame registration). The test PET scan will be aligned to the extracted subject MRI brain via a rigid registration algorithm. The aligned brain atlas will then be applied to the motion corrected PET dynamic data to generate time activity curves (TACs) of several brain regions, including (but not limited to) striatum, cortex, and cerebellum. The retest PET scan will be coregistered to the first scan and TACs will be generated using the previously defined ROIs for that subject.

At least the following analyses will be used for [^{11}C]MK-6884 binding quantification (index of M4 PAM receptor availability) in human brain from both test and retest scans:

a) Regional volumes of distribution (V_T) will be estimated by means of compartmental modeling and an arterial input function which represent the parent concentration of [^{11}C]MK-6884 in plasma. A one or two tissue compartment model will be selected on the basis of a model selection metric (e.g. AIC). Additional tests such as V_T time stability will also be performed to guide the selection of an appropriate scanning time and to support the development of simplified quantification techniques such as standardized uptake value ratios.

b) Non-displaceable binding potential (BP_{ND}) will be estimated for target M4 receptor rich region(s) based on tissue-ratio (transient equilibrium) method, as well as simplified reference tissue model (SRTM), with a suitable reference region that is devoid of M4 receptors. Based on preclinical studies in NHP PET and human brain autoradiography study, striatum (putamen and caudate) and cerebellum has been identified as the M4 receptor rich and poor regions, respectively. To validate the accuracy/bias in measurements, the BP_{ND} derived from both tissue-ratio method and SRTM will be compared to that derived from volumes of distribution. i.e. $V_T^{target}/V_T^{reference}$ -1.

c) Standardized uptake value ratio (SUV_R) will also be evaluated as part of the development of a simplified quantification strategy for [^{11}C]MK-6884. Standardized uptake value (SUV) represent the activity in the brain (or brain region) obtained during an specific time window normalized by total injected activity and whole body weight. SUV_R is a semi-quantitative measure of specific tracer uptake using a reference region which accounts for the non-displaceable signal present in the target region(s) (e.g. striatum).

$$SUV_R = \frac{SUV^{target}_{t_1,t_2}}{SUV^{reference}_{t_1,t_2}}$$

where $SUV^{target}_{t_1,t_2}$ and $SUV^{reference}_{t_1,t_2}$ are the standardized uptake values of the target and reference regions respectively between the times t_1 and t_2. SUV_R can be a surrogate for V_T or BP_{ND} where in static rather than dynamic scans are sufficient for quantifying M4 receptor availability. However, SUV_R can be of limited use as the data from reference region may be noisy because of low tracer uptake.

The test-retest variability (expressed in percentage) of the M4 receptor availability index (V_T or BP_{ND} or SUV_R) will be calculated by

$$T/RT\ variability\ =\ 2\frac{|Index^{test} - Index^{re-test}|}{Index^{test} + Index^{re-test}} \times 100$$

Less than 10% T-RT variability is ideal and less than 20% T-RT variability on average is acceptable for a PET tracer

d) If needed, additional methods may also be employed, to more robustly characterize the tracer kinetics in both healthy and AD subjects

Part III

Brain extraction and grey and white matter segmentation will be performed in each subject's MRI scan. A human brain atlas will be aligned to the extracted subject MRI brain via a non-linear registration algorithm.

[^{11}C]MK-6884 dynamic PET images will be corrected for decay, scatter, random coincidences, photon attenuation and motion (frame to frame registration). The PET scan will be aligned to the extracted subject MRI brain via a rigid registration algorithm. The aligned brain atlas will then be applied to the motion corrected PET dynamic data to generate time activity curves (TACs) of several brain regions, including (but not limited to) striatum, cortex, and cerebellum.

As AD subjects will undergo PET scans without arterial input function, the analyses that will be used for [^{11}C]MK-6884 binding quantification (index of M4 PAM receptor availability) in brain include BP_{ND} and/or SUV_R and will be determined as described in Part II. These parameters will be determined on an individual as well as on average basis.

Blood samples for AChE plasma concentration and RBC-AChE activity will be measured prior to [^{11}C]MK-6884 dosing. The information on plasma concentration and RBC-AChE activity will be used to explore quantitative relationships between BP_{ND} vs. plasma concentration and BP_{ND} vs. RBC-AChE activity using regression analysis or non-linear mixed effect modeling. The measured plasma concentration and RBC-AChE activity will

also be compared to pharmacokinetic/pharmacodynamics relationships described in the scientific literature, which may facilitate further analysis of the data.

8.2.5 Multiplicity

No multiplicity adjustment is needed. Only one of the hypotheses will be formally evaluated.

8.2.6 Power

Up to 26 (N=3-6 in Part I, N=6-10 in Part II, and N=7-10 in Part III) subjects will be included in the study. Given the investigational nature of this study no sample size calculation has been performed.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Table 9 Product Descriptions

Product Name & Potency	Dosage Form
[^{11}C]MK-6884 370 MBq (10 mCi) containing ≤4.9 µg MK-6884	A sterile solution

All other supplies not indicated in Table 9 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.2.1 Supply of Precursor and Synthesis/Labeling of [^{11}C]MK-6884

Merck Research Laboratories (MRL) will supply the local radiochemistry synthesis laboratory with the radiopharmaceutical precursor to MK-6884. [^{11}C]MK-6884 will be generated from the precursor compound after a final synthetic step.

MRL will also supply a nonradioactive version of MK-6884 to be used as an analytical standard during quality control procedures, and a Certificate of Analysis describing the precursor as well as the nonradioactive standard, will be provided.

Radiolabeling and sterile solution compounding will be conducted under the appropriate cGMP standards for clinical PET materials at this stage of development. The final compounded product will be in a sterile solution containing up to 10% (v/v) ethanol, 10 mM sodium phosphate buffer, pH 7 in 0.9% sodium chloride for injection. The radiopharmaceutical formulation will be prepared shortly before administration by the local radiochemistry synthesis laboratory. Unit doses that pass quality control procedures for radiochemical purity will be dispensed to physicians in the PET unit, using standard operating procedures for the production, transfer, and administration of radiopharmaceuticals.

A qualified staff member who is authorized to administer unsealed radioactive material to human beings may inject the radiopharmaceutical formulation intravenously after confirming that the batch passed all necessary quality control procedures and verifying that the radiation dose is correct.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted

standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results,

due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

1. Bodick NC, Offen WW, Levey AI, Cutler NR, Gauthier SG, Satlin A, Shannon HE, Tollefson GD, Rasmussen K, Bymaster FP, Hurley DJ, Potter WZ, Paul SM. Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. Arch Neurol. 1997 Apr;54(4):465-73.
2. Shekhar A1, Potter WZ, Lightfoot J, Lienemann J, Dubé S, Mallinckrodt C, Bymaster FP, McKinzie DL, Felder CC. Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. Am J Psychiatry. 2008 Aug;165(8):1033-9.
3. European Commission on Radiation Protection 99. Guidance on radiation exposures in medical and biomedical research. 1998; Directorate-General, Environment Nuclear Safety and Civil Protection.
4. Lilienfeld, S. Galantamine--a novel cholinergic drug with a unique dual mode of action for the treatment of patients with Alzheimer's disease. CNS Drug Rev. 2002 Summer;8(2):159-76.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of patient consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated

mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

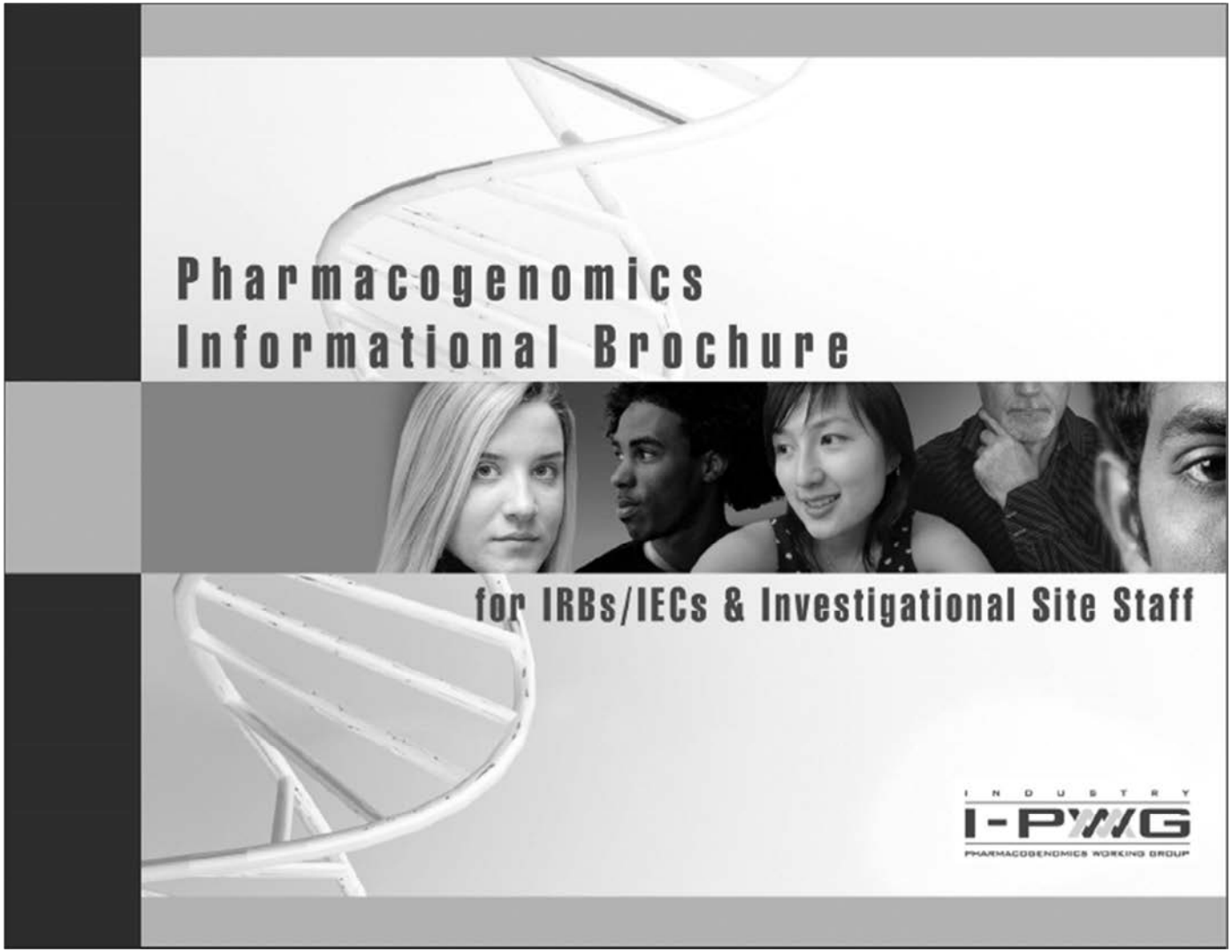
12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



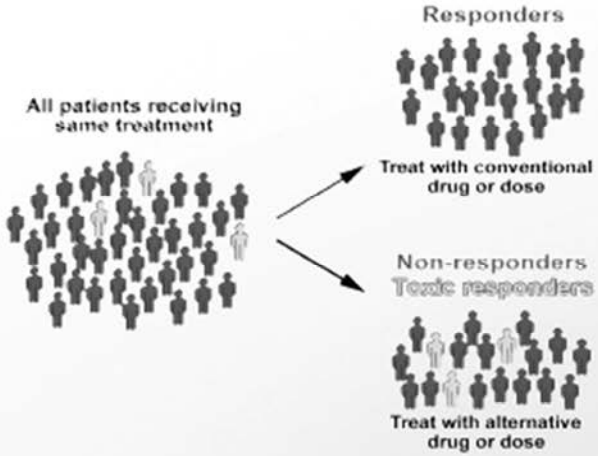
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid** (**DNA**). DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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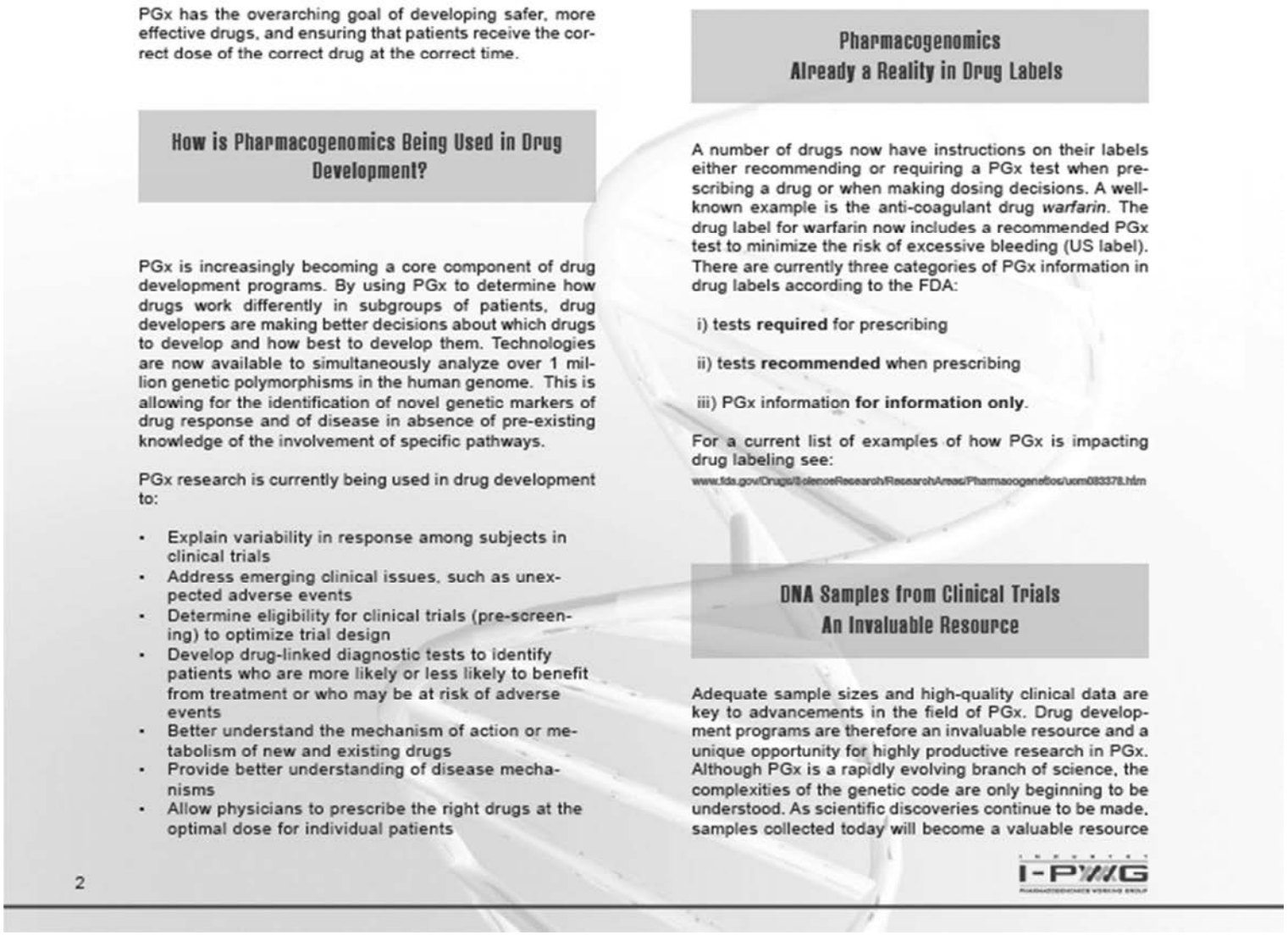

PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

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Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:

www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

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http://www.i-pwg.org

12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Part I	mL/collection	Number of draws	Total mL/ Test
Laboratory safety tests			
Screening	12.5	1	12.5
β-hCG or FSH (if applicable)	4.5	1	4.5
Pre-dose	12.5	1	12.5
Treatment	12.5	0	0
Post-study	12.5	1	12.5
Blood for Planned Genetic Analysis	8.5	1	8.5
HIV/Hepatitis Screen	5	1	5
Venous blood sampling (metabolite fraction in plasma)	4	6	24
Total Blood Volume Per Subject for Part I†			~ 79.5mL
Part II	**mL/collection**	**Number of draws**	**Total mL/ Test**
Laboratory safety tests			
Screening	12.5	1	12.5
PT/aPTT	2.5	1	2.5
β-hCG or FSH (if applicable)	4.5	1	4.5
Pre-dose	12.5	1	12.5
Treatment	12.5	0-2±	0-25
Post-study	12.5	1	12.5
Blood for Planned Genetic Analysis	8.5	1	8.5
HIV/Hepatitis Screen	5	1	5
Arterial Blood Sampling (for tracer metabolism-counts and metabolites in whole blood and plasma and metabolites in plasma)	4	12	48
Arterial Blood Sampling (for radioactivity in whole blood and plasma)	2	40	80
Total Blood Volume Per Subject for Part II†			~186mL to 211 mL
Part III	**mL/collection**	**Number of draws**	**Total mL/ Test**
Laboratory safety tests			
Screening	12.5	1	12.5
β-hCG or FSH (if applicable)	4.5	1	4.5
Pre-dose	12.5	1	12.5
Treatment	12.5	0	0
Post-study	12.5	1	12.5
Blood for donepezil or rivastigme plasma levels	4	1	4
Blood for erythrocyte-acetylcholinesterase activity	4	1	4
Blood for Planned Genetic Analysis	8.5	1	8.5
HIV/Hepatitis Screen	5	1	5
Total Blood Volume Per Subject for Part III†			~63.5 mL

† If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL..

± For Part II, if the second dose is done on a separate non-consecutive day, the number of blood draws during treatment will be 2 (and would require an additional 25 mL volume of blood).

12.5 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	**Potentially Significant Post-Randomization Findings (clarification on action to take)**
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥ 25 bpm from baseline and
Sinus Bradycardia	< 40 bpm	HR < 40 bpm and HR decrease of ≥ 5 bpm from baseline
Sinus Pause/Arrest	> 2.0 seconds	> 2.0 seconds
Atrial premature complex	> 1 beat	≥ 3 beats
Ventricular premature complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR < 40 bpm	Junctional Rhythm with HR < 40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB with Left Anterior Hemiblock (LAHB)	New onset LAHB
Right Axis Deviation	RBBB with Left Posterior Hemiblock (LPHB)	New onset LPHB
CONDUCTION		
1st degree A-V Block	PR ≥ 230 ms	PR ≥ 230 ms + increase of > 15 ms; or PR increase of > 25%
2nd degree A-V Block	Mobitz Type II	Mobitz Type II
3rd degree A-V Block	All	All
LBBB	All	All
RBBB	RBBB with LAHB/LPHB as defined above	New onset RBBB (not including intermittent or rate-related)
Incomplete Right BBB (ICRBBB) (QRS<120 ms)	No exclusion	Nothing

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	**Potentially Significant Post-Randomization Findings (clarification on action to take)**
Short PR/ Preexcitation syndrome	Delta wave + PR <120 ms	Delta wave + PR <120 ms
Other Intra-ventricular Conduction Delay	QRS ≥ 130 ms	QRS ≥ 130 ms + increase of ≥ 10 ms
QTc (B or F)		
Male	QTc ≥ 470 ms	QTc ≥ 500 ms or increase of ≥ 60 ms from baseline
Female	QTc ≥ 480 ms	QTc ≥ 500 ms or increase of ≥ 60 ms from baseline
HYPERTROPHY		
Atrial abnormalities	Definite evidence of P mitrale or P pulmonale	Definite evidence of P mitrale or P pulmonale
Ventricular abnor	Voltage criteria for LVH plus Strain Pattern	Voltage criteria for LVH plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST elevation suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST depression suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T changes (In 2 or more leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
Baseline is defined as Predose Day 1 ms=milliseconds, mm=millimeter		

12.6 Algorithm for assessing Out-of-Range laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or pre-dose evaluation:

A. If all protocol-specified laboratory values are normal, the subject may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the subject will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

   1. The subject may be excluded from the study;

   2. The subject may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

   3. The subject may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (*e.g.,* elevated eosinophil count in a subject with asthma or seasonal allergies) the medical condition should be annotated on the laboratory report or

   4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

      a. If the repeat test value is within the normal range, the subject may enter the study.

      b. If the repeat test value is still abnormal, the study investigator will evaluate the potential subject with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the subject may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the subject will be excluded from the study.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	