Supplementary Material

Structural Brain Magnetic Resonance Imaging to Rule Out Comorbid Pathology in the Assessment of Alzheimer's Disease Dementia: Findings from the Ontario Neurodegenerative Disease Research Initiative (ONDRI) Study and Clinical Trials Over the Past 10 Years

Supplementary Table 1. General Inclusion and Exclusion Criteria for ONDRI Study (Applicable to all diseases being studied)

Inclusion:	Exclusion:
Participants must meet each of the following criteria for enrolment into the study: 1. Written informed consent must be obtained and documented. 2. Participant must rate his/her level of proficiency in speaking and understanding English at 7 out of 10 or higher on the two LEAP-Q questions. 3. Participant must have ≥ 8 years education. 4. Participant with a minimum MoCA score of ≥18 (with the exception of FTD minimum score of ≥ 14) 5. Participant must have a reliable study partner. The study partner must: a. Interact regularly with the participant (i.e., have contact with the participant at least once a month over the phone, email, or face-to-face); b. Know the participant well enough to answer questions about the her/his cognitive abilities, communication skills, mood, and daily functioning (i.e., known the participant for at least 2 years); c. Provide written informed consent and complete study questionnaires; d. Be willing and able to assist in compliance with study procedures (if required). 6. Geographic accessibility to the study site. 7. Participant must be able to walk (assistive aids may be used,	Participants who exhibit any of the following conditions are to be excluded from the study: 1. Serious underlying disease other than the disease being studied which in the opinion of the investigator may interfere with the participant's ability to participate fully in the study. 2. Any disease that would/could lead to death over the next 3 to 5 years (i.e., cardiac/renal/liver cancer) with poor prognosis. 3. Participant has been diagnosed with more than one of the five diseases (AD/MCI, ALS, FTD, PD, or VCI) being studied. 4. History of alcohol or drug abuse, which in the opinion of the investigator, may interfere with the participant's ability to comply with the study procedures. 5. Presence of any of the following clinical conditions: a. Substance abuse within the past year. b. Unstable cardiac, pulmonary, renal, hepatic, endocrine, hematologic, or active malignancy or infectious disease. c. AIDS or AIDS-related complex. d. Unstable psychiatric illness defined as psychosis (hallucinations or delusions) or untreated major depression within 90 days of

e.g., cane, walker, etc.).	the screening visit. 6. Participant is currently enrolled in a disease modifying therapeutic (drug or interventional) trial or observational study that the Executive Committee feels would compromise study results. General Exclusion 7-12 applicable to London, Toronto and Ottawa only. 7. Participant has a known clinical diagnosis of glaucoma defined as taking eyedrops for glaucoma, or having had surgery for glaucoma in one or both eyes. Note: laser trabeculoplasty is an exclusion; however, yag laser iridotomy is permitted (i.e., not an exclusion). 8. Participant has any other known serious eye disease (e.g., wet/exudative age-related macular degeneration) or treatment or eye surgery including any history of intra-vitreal injections. Depending on the eye disease, the participant may be excluded if the condition is present in one or both eyes. The ocular part B platform lead should be consulted. 9. Participant has a known diagnosis of multiple sclerosis. 10. Participant has a known history of optic neuritis or other optic neuropathy in one or both eyes. 11. Participant has poorly controlled diabetes, defined by a hemoglobin A1c of 7.5% or higher obtained from the screening bloodwork. 12. Participant who has had known retinal laser therapy (either pan-retinal, or grid/focal) for diabetic retinopathy in one or both eyes.

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; LEAP-Q, Language Experience and Proficiency Questionnaire; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; VCI, vascular cognitive impairment

Supplementary Table 2. Diagnostic Criteria for Probable AD dementia

NINCDS-ADRDA	DSM-5	ICD-10
Probable Alzheimer's Disease Dementia: Core Clinical Criteria	**Major or Mild Neurocognitive Disorder Due to Alzheimer's Disease**	**Dementia in Alzheimer's Disease**
Meets criteria for dementia described earlier in the text [1], and in addition, has the following characteristics: A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days; B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories. a. Amnestic presentation: It is the most common syndromic presentation of Alzheimer's disease dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text. b. Nonamnestic presentations:	A. The criteria are met for major or mild neurocognitive disorder [2]. B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired). C. Criteria are met for probable Alzheimer's disease as follows: ***For major neurocognitive disorder:*** **Probable Alzheimer's disease** is diagnosed if either of the following is present; otherwise, **possible Alzheimer's disease** should be diagnosed. 1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing. 2. All three of the following are present: a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).	A. The general criteria for dementia (G1 to G4) must be met. B. There is no evidence from the history, physical examination or **special investigations for any other possible cause of dementia** (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus), a systemic disorder (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, hypercalcemia), or alcohol- or drug-abuse. The following features support the diagnosis, but are not necessary elements: Involvement of cortical functions as evidenced by aphasia, agnosia or apraxia; decrease of motivation and drive, leading to apathy and lack of spontaneity; irritability and disinhibition of social behavior; evidence from **special investigations that there is cerebral atrophy, particularly if this can be shown to be increasing over time**. In severe cases there may be Parkinson-like extrapyramidal changes, logoclonia, and epileptic fits.

• Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. • Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. • Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable Alzheimer's disease dementia should not be applied when there is **evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden**; or (b) core features of dementia with Lewy bodies other than dementia itself; or (c)	b. Steadily progressive, gradual decline in cognition, without extended plateaus. c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline). ***For mild neurocognitive disorder:*** **Probable Alzheimer's disease** is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history. D. **The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease**, the effects of a substance, or another mental, neurological, or systemic disorder.	

prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/ agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.		

Supplementary Table 3. Diagnostic Criteria for MCI

NIA-AA	DSM-5	ICD-10
Core Clinical Criteria	**Mild Neurocognitive Disorder**	**Mild cognitive disorder**
A. Concern about a change in cognition relative to previous functioning B. Impairment of one or more cognitive functions, like memory and problem solving, that is greater than expected for the person's age and education. (Memory is the function most commonly impaired among people who progress from mild cognitive impairment to Alzheimer's dementia.) C. Preserved ability to function independently in daily life, though some complex tasks may be more difficult than before D. No dementia	A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function, and 2. A modest impairment in cognitive performance, documented by standardized cognitive assessment B. The cognitive deficits do not interfere with capacity for independence in everyday activities (as measured by ADL scales), but greater effort, compensatory strategies, or accommodation may be required C. The cognitive deficits do not occur exclusively in the context of a delirium D. The cognitive deficits are not better explained by another mental disorder (e.g., psychosis and severe depression)	A. The general criteria for F06 must be met. B. The presence of a disorder in cognitive function for most of the time for at least two weeks, as reported by the individual or a reliable informant. The disorder is exemplified by difficulties in any of the following areas: (1) New learning (2) Memory (e.g., recall) (3) Concentration (4) Thinking (e.g., slowing) (5) Language (e.g., comprehension, word finding, etc.) C. Abnormality or decline in performance on neuropsychological tests (or quantified cognitive assessments). D. None of B (1)-(5) are such that a diagnosis can be made of dementia (F00-F03), amnesic disorders (F04), delirium (F05), postencephalitic syndrome (F07.1), postconcussional syndrome (F07.2), or other persisting cognitive impairment due to psychoactive substance use (F1x.74).

Supplementary Table 4. Neuroimaging-based Eligibility Criteria for AD Clinical Trials

ID	N	MRI Specified	Criteria
NCT00951834	21	x	Any condition disturbing or making MRI and other measures impossible
NCT01739348	2211	x	Participant does not have an MRI scan obtained within 12 months of screening and is unwilling or not eligible to undergo an MRI scan at the Screening Visit. With Sponsor approval, a head CT scan may be substituted for MRI scan to evaluate eligibility
NCT01782742	20	x	4 or more micro-hemorrhages (ARIA-H on baseline MRI or any evidence of ARIA-E [3]; Any contraindication of having brain MRI
NCT01715350	151		History and/or evidence (result of CT or MRI performed within the past 12 months or at screening) of other CNS disease (CVD, structural or developmental anomaly, epilepsy, contagious, degenerative or infectious/demyelinating CNS condition) as a cause of dementia
NCT01428453	124		A clinical diagnosis of possible AD in accordance with the NINCDS-ADRDA criteria, with radiological (MRI or CT) evidence of significant CVD, assessed within the last 12 months
NCT02260674	114	x	Participant has evidence of any brain disease, other than potential very early signs of AD (e.g., mild hippocampal atrophy) or typical age-related changes (e.g., mild white matter hyperintensity on MRI) or any other abnormality (e.g., folic acid/Vitamin B12 deficiency) that could explain a possible cognitive deficit (including, but not limited to vascular encephalopathy or strokes including lacuna's (as imaged by cerebral MRI) and Major Depression (as defined by most current Diagnostic and Statistical Manual of Mental Disorders criteria)
NCT00762411	1111		An MRI or CT scan in the last 2 years with no findings inconsistent with a diagnosis of AD
NCT00945672	36	x	Specific findings on MRI; cortical infarct, micro hemorrhage, multiple white matter lacunes, extensive white matter abnormalities.
NCT01227564	63	x	Contraindication to undergo brain MRI
NCT01626391	9	x	Patients in whom baseline MRI is contraindicated such as metal implants in head (except dental), pacemaker, and cochlear implant
NCT00675623	598		CT or MRI consistent with AD
NCT01374438	29	x	Inability to undergo a clinical (1.5T) MRI of the brain without contrast and lack of a usable (less the 12 months prior to screening) MRI on record. Contraindications to undergoing an MRI of the brain include, but are not limited to, pacemakers; implantable cardioverter defibrillators; cochlear implants; cerebral aneurysm clips; implanted infusion pumps; implanted nerve stimulators; metallic splinters in the eye; and, other magnetic, electronic or mechanical implants or clinical findings that in the judgment of the investigator would pose a potential hazard in combination with MRI.
NCT01068353	41		Signs of major CVD on MRI or CT scan, if performed prior to entry into study (i.e., presence of infarction in greater than 25% of white matter, more than 1 lacune within basal ganglia, more than 2 lacunes in white matter)

NCT01689233	800	x	Significant focal or vascular intracranial pathology seen on brain MRI scan; Metal implants in the head (except dental), pacemaker, cochlear implants, or any other non-removable items that are contraindications to MRI
NCT01689246	891	x	Significant focal or vascular intracranial pathology seen on brain MRI scan
NCT00722046	198	x	Specific findings on MRI; cortical infarct, micro hemorrhage, multiple white matter lacunes, extensive white matter abnormalities
NCT02760602	26	x	Has had MRI or CT of brain within previous 2 years showing pathology that would be inconsistent with a diagnosis of AD; Has screening MRI with results showing >4 ARIA-H micro-hemorrhages or presence of ARIA-E; Has any contraindications for MRI studies, including claustrophobia, the presence of metal (ferromagnetic) implants, or a cardiac pacemaker that is not compatible with MRI.
NCT02240693	128		MCI with any etiology other than prodromal AD (for example: neurosyphilis, craniocerebral trauma, small vessel disease) based on clinical data and/or current laboratory findings and/or a pre-existing MRI or CT of the brain (CCT). If previous cranial imaging is not available or older than 12 months prior to screening then a CCT or MRI needs to be performed at screening
NCT02389413	120	x	History of or screening visit brain MRI scan indicative of any other significant abnormality.
NCT00842673	168		CT or MRI results within the past 12 months that rule out dementia due to non-AD etiology.
NCT00678431	27		CT or MRI since onset of memory impairment demonstrating absence of clinically significant focal lesion (One lacune in a non-critical brain region is acceptable)
NCT00842816	210		CT or MRI results within the past 18 months that rule out dementia due to non-AD etiology.
NCT01284387	126	x	Brain MRI scan consistent with the diagnosis of AD
NCT01900665	2129	x	Has had an MRI or CT scan performed within the past 2 years that has confirmed no findings inconsistent with a diagnosis of AD; Has a Visit 1 MRI with results showing >4 ARIA, ARIA-H, or presence of ARIA-E
NCT02064920	36	x	Has an MRI scan that rules out non-AD conditions contributing to cognitive dysfunction; Is unwilling or ineligible to undergo an MRI scan; Has a history of clinically important structural changes on screening MRI scan
NCT01736579	6	x	Contraindication to undergoing MRI (e.g., pacemaker [with the exception of an MRI-compatible pacemaker], severe claustrophobia, ferromagnetic implants such as a metal plate); Specific findings on brain MRI (microhemorrhages, superficial siderosis, vasogenic edema, a macrohemorrhage, major stroke, or multiple lacunae)
NCT01662882	48	x	One or more of the following findings on a MRI scan: Multiple (two or more) infarcts or white matter lacunes; A single large infarct or a strategically placed infarct in the angular gyrus, the thalamus, the basal forebrain, the posterior cerebral artery or anterior cerebral artery territory; Any evidence on screening MRI, CT, or other biomarker studies that suggests an alternate etiology (other than probable AD in subjects with AD) for cognitive deficit; or in the case of cognitively normal controls any evidence on screening MRI, CT, or other biomarker studies that suggests the presence of AD pathology
NCT01852110	240	x	Does not have an MRI scan obtained within 12 months of Screening and is unwilling or not eligible to undergo an MRI scan at Screening
NCT01428362	61		CT or MRI within 2 years prior to study
NCT01009255	196		Has undergone MRI or CT scan in the last 12 months. (For subjects not meeting this criteria, as scan will be conducted as part of the screening procedures); In the opinion of the investigator, following review of CT/MRI scans in the past 12 months and completion of neurological review there could be other probable causes of dementia

			which include, but are not limited to: History and/or evidence (CT or MRI scan performed since the onset of symptoms) of any other CNS disorder that could be interpreted as the primary cause of dementia: e.g., CVD, structural or developmental abnormality, epilepsy, infections, degenerative or inflammatory/demyelinating CNS conditions other than AD.
NCT01524887	508	x	Neuroimaging (CT or MRI) performed after symptom onset consistent with AD diagnosis; Contraindication to undergoing MRI (e.g., pacemaker [with the exception of an MRI-compatible pacemaker], severe claustrophobia, ferromagnetic implants such as a metal plate); Evidence on MRI of: greater than 4 microhemorrhages (regardless of their anatomical location or diagnostic characterization as "possible" or "definite"), a single area of superficial siderosis, vasogenic edema, a macrohemorrhage, major stroke, prominent white matter disease with a rating score of 3 on the ARWMC scale from the European Task Force on ARWMC, or multiple lacunae (defined as more than 2 lacunae that are greater than 0.5 mm in size)
NCT01324518	100		Brain imaging consistent with AD; Specific findings in brain imaging
NCT01388478	20		Imaging Study (CT or MRI) compatible with AD or age-related changes (absence of significant abnormalities that may explain cognitive decline, such as multiple lacunar infarcts or a single prior infarct >1 cubic cm, microhemorrhages or evidence of a prior hemorrhage > 1 cubic cm, evidence of cerebral contusion encephalomalacia, aneurysm, vascular malformation, or space occupying lesion such as an arachnoid cyst or brain tumor).
NCT01712074	186		Clinical diagnosis of probable AD with supportive brain imaging documentation
NCT01399125	501		have a brain scan (MRI or CT) consistent with the diagnosis of AD. The brain scan must have been performed within one year prior to randomization;
NCT00904683	1040	x	An MRI or CT scan in the last 2 years with no findings inconsistent with a diagnosis of AD; Has any contraindications for MRI studies
NCT00880412	197		Patient with a cerebral CT-scan or cerebral MRI compatible with AD diagnosis, with no brain lesions that may be related to another diagnosis and that could be responsible for the current patient's condition (ex, but not limited to, non-AD dementia, brain injury, brain tumor, stroke, normal pressure hydrocephalus, etc.). A cerebral CT-scan or cerebral MRI has to be performed and results have to be available prior patient's randomization if the results of the brain imagery performed to settle the AD diagnosis are not available in the patient's file. Brain imaging has also to be performed if considered necessary by the investigator, such as in case of emerging neurological symptoms or in case of worsening of existing neurological symptoms.
NCT00905372	1000	x	An MRI or CT scan in the last 2 years with no findings inconsistent with a diagnosis of AD; Has any contraindications for MRI studies
NCT01254773	146	x	Brain MRI scan consistent with the diagnosis of AD
NCT01019421	278		The patient has CT or MRI evidence of hydrocephalus, stroke, a space-occupying lesion, cerebral infection or any clinically significant CNS disease other than AD.
NCT01117948	219		Clinical, laboratory or neuroimaging findings consistent with: other primary degenerative dementia (dementia with Lewy bodies, FTD, Huntington's disease, Creutzfeldt–Jakob disease, Down's syndrome, etc.) other neurodegenerative condition (Parkinson's disease, amyotrophic lateral sclerosis, etc.) CVD (major infarct, one strategic or multiple lacunar infarcts, extensive white matter lesions > one quarter of the

			total white matter) other CNS diseases (severe head trauma, tumors, subdural hematoma or other space occupying processes, etc.) seizure disorder other infectious, metabolic or systemic diseases affecting CNS (syphilis, present hypothyroidism, present vitamin B12 or folate deficiency confirmed by current analyses not older than 1 month, serum electrolytes out of normal range, juvenile onset diabetes mellitus, etc.)
NCT00818662	390	x	Neuroimaging (CT or MRI) performed after symptom onset consistent with AD diagnosis; Evidence of current bleeding in the brain by MRI
NCT01018875	242		Subject has a CT or MRI scan within 36 months prior to randomization.
NCT00749216	33	x	Patients who have an MRI or CT scan since the onset of symptoms of AD that is inconsistent with a diagnosis of AD; Patients who have any contraindications for MRI studies, including claustrophobia, the presence of metal (ferromagnetic) implants, or cardiac pacemaker.
NCT02471196	308		Brain imaging (CT or MRI) consistent with a diagnosis of AD (within 18 months or at screening); Specific findings in MRI or CT that could in the opinion of the investigator affect cognitive function (such as cortical infarct or silent lacuna in a region known to affect cognition).
NCT00960531	160	x	Screening brain MRI scan is consistent with the diagnosis of AD.
NCT01117818	335	x	Brain MRI scan consistent with the diagnosis of AD; Contraindication for MRI scan
NCT00955409	50	x	Screening brain MRI scan is consistent with the diagnosis of AD; Brain MRI evidence of vasogenic edema during the preceding 3134K1 200 study (NCT00479557)
NCT00594568	1537		An MRI or CT scan in the last 2 years with no findings inconsistent with a diagnosis of AD
NCT00855868	28	x	AD subjects: MMSE 18-26, Clinical Dementia Rating ≥0.5, University of Pennsylvania Alzheimer's Disease Center consensus diagnosis of probable AD, absence of abnormalities on MRI; evidence of MRI abnormality
NCT00672945	420		Brain CT or MRI scan Consistent with a primary diagnosis of AD within 24 months
NCT00693004	236		Brain CT or MRI scan Consistent with a primary diagnosis of AD within 12 months
NCT02423200	16	x	Inability for any reason to undergo MRI scans (e.g., pacemaker, vascular stent or stent graft). Patients who require sedation for screening procedures such as MRI may receive a short-acting sedative.
NCT00676143	1100	x	Diagnosis of probable AD, with MMSE score of 16-26, and brain MRI consistent with the diagnosis of AD; Contraindication to undergo brain MRI (e.g., pacemaker, CSF shunt, or foreign metal objects in the body)
NCT00667810	901	x	Diagnosis of probable AD, with MMSE score of 16-26, and brain MRI consistent with the diagnosis of AD; Contraindication to undergo brain MRI (e.g., pacemaker, CSF shunt, or foreign metal objects in the body)
NCT01741194	418		CT or MRI scan within 18 months prior to screening compatible with a diagnosis of probable AD; An alternative cause for dementia other than AD as determined by a required CT or MRI scan within 18 months prior to screening
NCT00785759	78	x	The subject has a contraindication for MRI (including, but not limited to, claustrophobia, pacemaker, presence of metallic fragments near the eyes or spinal cord, or cochlear implant).
NCT00812565	58	x	MRI of the head consistent with the diagnosis of AD.
NCT01466088	386		AD diagnosed at least 12 months prior to Screening, and supported by brain imaging studies within 6 months prior to Screening.

NCT01969136	403		MRI or CT scan performed within 12 months before screening, with findings consistent with the diagnosis of dementia due to AD without any other clinically significant comorbid pathologies. If an MRI or CT scan is unavailable or occurred greater than 12 months before screening, this assessment should be completed and the findings confirmed before the subject enters the run-in period (Day -14) (copy of the report will be available at the study site); History of brain tumor, subdural hematoma, or other clinically significant (in the judgment of the investigator) space-occupying lesion on CT or MRI
NCT01969123	474		MRI or CT scan performed within 12 months before screening, with findings consistent with the diagnosis of dementia due to AD without any other clinically significant comorbid pathologies. If an MRI or CT scan is unavailable or occurred greater than 12 months before screening, this assessment should be completed and the findings confirmed before the subject enters the run-in period (Day -14) (copy of the report will be available at the study site); History of brain tumor, subdural hematoma, or other clinically significant (in the judgment of the investigator) space-occupying lesion on CT or MRI
NCT00843518	132		Have an MRI or CT scan on file since the onset of symptoms of AD and performed within the past 24 months that is inconsistent with a diagnosis of AD.
NCT00750282	422	x	Healthy Volunteers: Has MRI brain scan that has been judged as "normal" (age- appropriate); AD: MRI brain scan findings that do not reveal changes indicative of stroke and/or generalized CVD; Has any contraindication to MRI examination scan
NCT01463384	13	x	Any person with medical devices such as cardiac pacemakers/defibrillators or neuro-implants as they are contra-indications for MRI/MRS exam; Since the effects of MRI are unknown to the fetus or unborn child, any person who is or may be pregnant will be excluded from the study.
NCT01436045	12		A brain CT or MRI in the last 2 years compatible with the diagnosis of probable AD;
NCT01028053	365	x	The subject has a non-contrast MRI examination as part of the screening visit that excludes aMCI arising from structural causes; The subject has one or more aneurysm clips, artificial heart valves, metal implants, embedded metal fragments or pacemakers that would pose a risk during an MRI.
NCT02361424	47	x	MRI assessment which corroborates the clinical diagnosis (hippocampal atrophy) and excludes other potential causes of dementia especially cerebrovascular lesions
NCT01764243	450		MRI or CT scan within 6 months before screening, with findings inconsistent with the diagnosis of Probable AD
NCT01453569	255		Significant focal lesions revealed by CT or MRI in one year before enrollment.
NCT01681602	200		Imaging (CT or MR of cerebrum) consistent with AD; Severe CVD judged from the CT or MR scans and remarkable hypertension defined as Systolic blood pressure >180 and diastolic >100
NCT01661673	52		MRI/CT scans compatible with diagnosis of MCI or early AD
NCT01249196	256	x	MRI within the last 12 months consistent with a diagnosis of AD
NCT00940589	73		Cranial image: no evidence of focal disease to account for dementia (established by CT, PET or MRI). If there is no such available scan (CT, PET or MRI), one must be performed prior to enrollment.
NCT01404169	260		Evidence of focal disease to account for dementia on any cranial image MRI or CT.
NCT00663026	79	x	MRI showing other brain abnormalities
NCT01539031	351		No evidence of focal disease to account for dementia on any cranial image (MRI or CT);

NCT02245568	913	x	Clinically significant laboratory, pulse co-oximetry, electrocardiogram, or imaging abnormality (in originating study) or emergent intercurrent illness that, in the judgment of the principal investigator, could result in the risk of participation outweighing the potential benefit; Significant focal or vascular intracranial pathology seen on brain MRI scan; Metal implants in the head (except dental), pacemaker, cochlear implants, or any other non-removable items that are contraindications to MRI; Patients in whom baseline MRI is contraindicated such as metal implants in head (except dental), pacemaker, and cochlear implant
NCT01890343	34		Evidence from MRI or other biomarkers that suggests an etiology of dementia other than AD or FTD, as applicable or in the case of control subjects evidence indicating the presence of AD, FTD or other types of neurologic pathology
NCT01276353	45		Evidence consistent with AD on any cranial image on MRI or CT scan or etc. obtained within 24 months prior to the Screening Visit. Subjects who have any observations of dementia other than Alzheimer's type after the last image diagnosis should be reconfirmed.
NCT01020838	218	x	Is willing and able to lie down in MRI and PET scanners; The subjects who have participated in a previous florbetaben study, e.g., study 311741 may be included in the present study. The MRI- and florbetaben PET scan do not need to be repeated if both scans were performed within twelve months prior to inclusion.; Has severe cerebral macrovascular (i.e., multi-stroke) disease or brain tumor (metastasis/brain cancer) as verified by MRI; Has any contraindication to MRI examination, e.g., metal implants or phobia as determined by the onsite radiologist performing the scan
NCT00814346	49	x	Contraindication to MRI and/or PET scan
NCT01058941	67	x	Contraindications to MRI (for subjects enrolled at Bend, Medford, and Klamath sites that decide not to undergo MRI, this will not be an exclusion).
NCT01560585	10		Neuroimaging (CT or MRI or PET) consistent with the diagnosis of AD at some time after the onset of the memory decline.
NCT02423122	16	x	Inability for any reason to undergo PET and functional MRI scans (including notably: history of allergic reaction of any severity to ^{11}C-PiB injection; pacemaker, vascular stent or stent graft)
NCT01607476	89	x	Standard safety exclusionary criteria for MRI such as metallic foreign bodies, pacemaker, etc.
NCT01303744	96	x	MRI scan of the brain at screening with fluid-attenuation inversion recovery and T2*-weighted gradient-recalled-echo sequences; CT or MRI brain imaging results obtained within 12 months prior to baseline showing evidence of infection, infarction, or focal lesions of clinical significance; MRI scan at screening showing more than 4 cerebral microhemorrhages (lesions with diameter $\leq$ 10 mm).
NCT01577394	65	x	Contraindication for MRI examination
NCT02221947	9	x	Significant neuroimaging abnormalities, previously known or discovered on screening MRI scan
NCT01142258	40		CT or MRI since the onset of memory problems showing no more than 1 lacunar infarct in a nonstrategic area and no clinical events suggestive of stroke or other intracranial disease or normal
NCT00580931	50		Brain imaging (CT scan or MRI) within 12 months consistent with a diagnosis of probable AD
NCT00948259	30		MRI or CT-scan assessment within 12 months before baseline corroborating the clinical diagnosis (diffuse brain atrophy predominating in medial temporal regions) and excluding other potential causes of dementia, especially cerebrovascular lesions (see exclusion criteria, number 3); Clinical, laboratory or neuroimaging findings consistent with:

			other primary degenerative dementia, (dementia with Lewy bodies, frontotemporal dementia, Huntington's disease, Creutzfeldt–Jakob disease, Down's syndrome, etc.) other neurodegenerative condition (Parkinson's disease, amyotrophic lateral sclerosis, etc.) CVD (major infarct, one strategic or multiple lacunar infarcts, extensive white matter lesions) other CNS diseases (severe head trauma, tumors, subdural hematoma or other space occupying processes, etc.) seizure disorder other infectious, metabolic or systemic diseases affecting CNS (syphilis, present hypothyroidism, present vitamin B12 or folate deficiency, serum electrolytes out of normal range, juvenile onset diabetes mellitus, etc.)
NCT01354691	201		MRI or CT assessment within 6 months before baseline, corroborating the clinical diagnosis and excluding other potential causes of dementia especially cerebrovascular lesions
NCT00857415	226	x	Evidence of brain abnormality on an MRI scan;
NCT01513967	36		MRI or CT within 12 months of Screening visit consistent with a diagnosis of probable AD without any other clinically significant findings
NCT02813070	70	x	The subject had an MRI image as part of the screening visit of sufficient diagnostic quality and consistent with normal brain function (details provided in the associated Imaging Manual) for VOI definition and partial volume correction; The subject had an MRI image as part of the screening visit consistent with the diagnosis of probable AD and of sufficient diagnostic quality (details provided in the associated Imaging Manual) for VOI definition and partial volume correction; The subject had an MRI image as part of the screening visit consistent with the diagnosis of aMCI and of sufficient diagnostic quality (details provided in Imaging Manual) for VOI definition and partial volume correction; The subject had a contraindication for MRI or PET (including, but not limited to, claustrophobia, pacemaker, the presence of metallic fragments, or cochlear implant).
NCT02149017	30	x	any present serious medical, psychiatric, or neurological disorder that could affect mental function; evidence of focal brain lesions on MRI; the presence of severe behavioral or communication problems
NCT01922258	270		Subjects must have a previous MRI or CT scan of the brain, which was performed after the onset of symptoms of dementia, with findings consistent with the diagnosis of AD.
NCT01862640	433		Subjects must have a previous MRI or CT scan of the brain, which was performed after the onset of symptoms of dementia, with findings consistent with the diagnosis of AD.
NCT01503944	30		Have evidence from MRI or other biomarker studies that suggests the presence of a CNS pathology other than that associated with the study diseases
NCT01965756	20	x	positive topographic (MRI, FDG-PET) or molecular (CSF, amyloid imaging) biomarker consistent with AD; Screening/baseline MRI scans with evidence of infarction or other focal lesions in critical memory structures that may be related to cognitive dysfunction; Pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body or claustrophobia that would preclude MRI scanning
NCT01780974	42	x	Contraindications to MRI, including: subjects with intrathecal pumps, stimulators, pacemakers, aneurysm clips, non-removable hearing aids, or metal fragments in the eyes. Other exclusion criteria include the inability to lie flat on the back for 40 minutes at a time or a self-reported history of claustrophobia. Subjects with a history of hip replacement and those with well-documented, verifiable, MRI-safe cardiac stents will not be excluded from the study.
NCT00701532	29	x	Contraindications for modafinil and MRI
NCT01429623	210	x	All patients have to undergo an MRI scan after the screening visit, i.e., during the screening visit, irrespective of MRIs having been performed prior to entry into the study. MRI findings have to be consistent with a diagnosis of

			MCI; MRI exclusion criteria which allow for mild concomitant vascular lesions are: Thromboembolic infarction Other focal lesions which may be responsible for the cognitive status of the patient such as infectious disease, space-occupying lesions, normal pressure hydrocephalus or any other abnormalities associated with significant CNS More than one lacunar infarct defined as a focal lesion of CSF signal intensity with a diameter of <1.5 cm in any dimension Any lacunar infarct in a strategically important location such as the thalamus, hippocampus of either hemisphere, head of the left caudate White matter lesions involving more than 25% of the hemispheric white matter Implants such as pacemakers, insulin pumps, cochlear implants, nerve stimulators, implantable cardioverter defibrillators, and other medical implants that have not been certified for MRI Ferromagnetic foreign bodies such as shell fragments need to be considered on an individual basis Metallic implants that can cause artifacts and RF induced heating such as surgical prostheses or aneurysm clips need to be considered on an individual basis
NCT01482351	86	x	Willing to undergo MRI and provide DNA for ApoE4 assessments; Any MRI exclusions - presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin, or body
NCT01044758	96	x	Medical contraindications to MRI including cardiac pacemaker, presence of intraocular or intracranial metallic objects

AD, Alzheimer’s disease; aMCI, amnestic mild cognitive impairment; ARIA-E, amyloid-related imaging abnormalities - effusion type; ARIA-H, amyloid-related imaging abnormalities - hemorrhage type; ARWMC, age-related white matter changes; CVD, cerebrovascular disease; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; FTD, frontotemporal dementia; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; PET, positron emission tomography; VOI, volume of interest

REFERENCES

[1] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263–269.

[2] American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association, Arlington, VA.

[3] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 280-292.