Assessment of Safety, Tolerability, and Pharmacodynamic Effects of LY2886721 in Patients with Mild Cognitive Impairment Due to Alzheimer*s Disease or Mild Alzheimer's Disease

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mental impairment disorders
Study type	Interventional

Summary

ID

NL-OMON39447

Source
ToetsingOnline

Brief title
Eli Lilly I40 MC BACC

Condition

- Mental impairment disorders

Synonym
Alzheimer's Disease, Dementia

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Alzheimer's Disease, LY2886721, Phase 1B/2

Outcome measures

Primary outcome

The primary objective:

To assess the cerebrospinal fluid (CSF) pharmacodynamic (FD) effect of

different LY2886721 doses in patients with mild cognitive impairment (MCI) due

to Alzheimer*s Disease (AD) or mild AD compared to placebo, measured by change

of CSF Aβ1-40 and Aβ1-42 concentrations from baseline to Week 12 and Week 26.

Secondary outcome

The secondary objectives:

• To assess safety and tolerability of LY2886721 over 26 weeks

• To compare cerebral vasogenic edema (ARIA-E) and cerebral microhemorrhage

(ARIA-H) using fluid attenuation inversion recovery (FLAIR) and T2*w MRI

associated with different doses of LY2886721 treatment or placebo

• To assess the plasma PD effect of different LY2886721 doses compared to

placebo, measured by change

of plasma Aβ1-40 and Aβ1-42 concentrations from baseline to Week 12 and 26

• To assess the effect of 2 doses of LY2886721 compared to placebo on the

cognitive and behavioral

symptoms of AD measured by:

- Neuropsychological Test Battery (NTB)

- AD Assessment Scale - Cognitive subscale (ADAS-cog)

- Mini Mental State Examination (MMSE)

- Neuropsychiatric Inventory (NPI).

• To assess the effect of 2 doses of LY2886721 compared to placebo on the

global rating of symptoms of

AD measured by the Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB).

• To assess change from baseline to Week 12 and 26 for cSF tau and ptau181.

Study description

Background summary

Alzheimer*s disease (AD), a serious global health problem, is a degenerative disease affecting
older people that results in the slow decline of cognitive and behavioral functions with a
characteristic symptom of memory loss in patients. Therapies that have been developed so far to treat AD are able to reduce only the symptoms of AD without affecting the
underlying pathology of the disease, so patients continue to clinically decline.

After autopsy, patients with AD routinely display severe brain atrophy with neurofibrillary tangles and amyloid plaques. Although the definitive cause of the disease is not yet clearly understood, evidence continues to mount that amyloid beta (Aβ)

peptide is a culprit that aggregates to form amyloid plaques. These plaques are toxic to neurons and are believed to lead to synapse loss and eventual neuronal cell death.
Hence, inhibition of Aβ formation is a logical strategy towards developing a therapy for AD that may
be effective in slowing the diseaseprogression.

Amyloid β (Aβ) is part of the amyloid precursor protein (APP). It is a transmembrane protein
widely expressed on the cell surface, particularly in neurons. APP has been found to be cleaved
through 2 cleavage pathways involving 3 secretase enzymes: α-secretase, γ-secretase, and β-
secretase. In one pathway, β-secretase cleaves the APP molecule,
generating membrane-associated C99 and releasing a shorter secreted fragment called sAPPβ.
γ-Secretase then cleaves C99 in a heterogeneous fashion within the membrane, releasing Aβ1-40
and the toxic Aβ1-42 species, which aggregate in protofibrils, then fibrils, which seem to comprise
the mass of Aβ plaques in AD brain tissue.

LY2886721 is a synthetic small molecule β-site amyloid precursor protein cleaving enzyme
(BACE) inhibitor. In vitro, in vivo and clinical studies showed that LY2886721 administration results in a
decrease of Aβ plasma and/or CSF levels. Moreover, the previously performed clinical trails demonstrate
that daily doses up to 35 mg LY2886721 was well tolerated.

Study objective

Assessment of Safety, Tolerability, and Pharmacodynamic Effects of LY2886721 in Patients with
Mild Cognitive Impairment Due to Alzheimer*s Disease or Mild Alzheimer's Disease

Study design

Phase 2, parallel, randomized, placebo-controlled, double-blind study comparing daily dosing of
LY2886721 to placebo over a 26-week period for the treatment of MCI due to AD or mild
AD. The 26-week double-blind study will be followed with a 2-week follow up. Participation in CSF collection at
baseline and 1 postbaseline time point is mandatory for all sites and patients.

Intervention

Taking (oral) investigational product.

Study burden and risks

- In a toxicity study in rats, adverse eye findings occurred. They consisted of increased autofluorescent granules dispersed throughout the cytoplasm of individual retinal epithelial cells. In some cases this change was accompanied by enlarged retinal epithelial cells and degeneration of the outer photoreceptor layer.

- CNS effects consisting of tremor and convulsion in rats and dogs

- Hyper-reactivity and decreased activity in rats

- During previous clinical trials with LY2886721, subjects reported (regardless of causality) headache, dizziness, nausea, gingivitis, oral herpes, viral infection, decreased blood pressure, decreased libido, chest pain, muscle spasm, sinus congestion and abnormal visual field.

- Side-effects of Lumbar puncture: possible headach, back pain and stiffness

- Side-effects of eye tests: Pupil dilation, blurred vision

- Being injected with radioactive substance (Florbetapir F18) and radiation (PET Scan)

- Discomfort (blood draw, ECG, MRI)

- Patients undergo intensive screening (more than one day)

- Patients undergo psychological and neuropsychological tests

- Patients must bring a caregiver to each appointment

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria:
Patients may be included in the study only if they meet all of the following criteria:
[1] Present with MCI due to AD or mild AD based on the disease diagnostic criteria (Section 8.1.1).
[2] Are men or postmenopausal women, at least 55 years of age. Postmenopausal women are defined as women who have had a hysterectomy and/or bilateral oophorectomy; or who have been amenorrheic for at least 2 years.
[3] Have a reliable caregiver/study informant who provides a separate written informed consent to participate and who is in frequent contact with the patient (defined as at least 10 hours per week). The caregiver/study informant must be able to communicate with site personnel and in the investigator*s opinion must have adequate literacy to complete the protocol-specified questionnaires. If a caregiver/study informant cannot continue, 1 replacement is allowed.
[4] Have adequate vision (have not met exclusion criteria 12) and hearing for neuropsychological testing in the opinion of the investigator
[5] Have adequate premorbid literacy in the investigator*s opinion to complete the required psychometric tests
[6] Have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site

Exclusion criteria

Exclusion Criteria:
Subjects will be excluded from the study if they meet any of the following criteria:
[7] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the investigational product used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
[8] Diagnosis or history of other possible etiology of dementia, including but not limited to other neurodegenerative disorders
[9] Has received acetylcholinesterase inhibitors (ACHEIs), memantine and/or other AD therapy for <2 months or has <4 weeks of stable therapy on these treatments by Visit 1, or, in the opinion of the investigator, the patient will not likely remain on stable treatment regimen for 6 months. Note: If a patient has recently stopped ACHEIs and/or memantine, he or she must have discontinued treatment at least 4 weeks before Visit 1. Patients not treated with anti-Alzheimer drugs are eligible for study enrollment.
[10] Has frontotemporal dementia, Lewy body disease, vascular dementia, Huntington*s Disease or concomitant Parkinson*s disease, progressive supranuclear palsy (PSNP) or other movement disorder, or active autoimmune or neuroimmunologic disorders causing dementia or cognitive impairment
[11] Has B12 <200 pg/ml (<148 pmol/L), or folate <7.5 nmol/L (<3.3 ng/ml) indicating vitamin deficiency
[12] Patients with significant retinal impairment:
morphological retinal impairment (based on the 3-field visual photography and, OCT).
• significant (moderate or severe) dry or any untreated wet age-related macular degeneration.
• other significant retinal diseases (such as diabetic retinopathy),
• retinal vascular occlusions that are visually significant
• clinically significant epiretinal membrane (or macular pucker) or a clinically significant macular hole
functional impairment, such as:
• corrected visual acuity less than 20/40 in each eye, as measured on the Snellen, ETDRS or equivalent chart
• VFQ-25, with a baseline global score of less than 70
• increased intraocular pressure (non-treated glaucoma)
Opthalmological diagnostic and exclusion criteria will be defined in Manual of Operations provided to the sites.
[13] Has a history within the past 5 years of a serious infectious disease affecting the brain, including meningitis, or encephalitis
[14] Severe or recurrent head injury that is clinically relevant to the disease under study, (that is, with permanent neurological/cognitive sequelae)
[15] Onset of dementia following heart surgery or cardiac arrest
[16] Abnormal thyroid function: Thyroid Stimulating Hormone (TSH) values are outside of the normal range 0.3-5.6 mIU/L. (NOTE: patients with stable treatment of hypothyroidism and with normal value of TSH will be allowed to enter the study).
[17] Diagnosis or history of cerebrovascular disease (for example, stroke, transient ischemic

attack), severe carotid stenosis, cerebral hemorrhage, intracranial tumor, subarachnoid hemorrhage, or subdural hematoma that could contribute to the subject's current cognitive or functional status, impair ability to fully participate in the trial or that may impact health status.
[18] Has had a PET scan within 6 months of the scheduled imaging at Visit 2;[19] Are being monitored for radiation due to occupational exposure to ionized radiation, or exposure to ionizing radiation within the last 12 months from an investigational study
[20] Greater than 4 ARIA-Hs on T2* weighted gradient recalled echo sequences (regardless of their anatomical or diagnostic characterization as *possible* or *definite*), a single area of superficial siderosis, or prior evidence of macrohemorrhage.
[21] Any indications of ARIA-E or severe deep white-matter lesions that present as hyperintense regions on the FLAIR sequence on the Visit 2 MRI scans
[22] Specific exclusionary or clinically relevant brain MRI findings, as determined by the investigator in consultation with the Sponsor, as necessary), that could either contribute to the patient's current cognitive or functional decline, impair ability to fully participate in the trial, or that may impact status during the trial (for example, brain tumors or other nonvascular structural abnormalities like hydrocephalus) based on a local reading of MRI
[23] History within the past 5 years of a primary or recurrent malignant disease with the exception of resected cutaneous squamous cell carcinoma in situ, basal cell carcinoma, cervical carcinoma in situ, or in situ prostate cancer with a normal prostate specific antigen (PSA) postresection.
[24] History of clinically significant cardiovascular or renal events
[25] Diastolic blood pressure >=95 and systolic blood pressure >=160 in sitting position after at least 5 minutes of rest
[26] Any history of seizure. (Note: Patients who experienced a febrile seizure during childhood may participate.)
[27] History of clinically significant head trauma or clinically significant unexplained loss of consciousness within the last 5 years (as determined by the investigator in consultation with the Sponsor)
[28] Having major depression according to Mini International Neuropsychiatric Interview (MINI) depression module OR having psychiatric illness at baseline defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV) text revision (TR) criteria per the investigator's judgment. (Note: Patients on a stable antidepressant and/or anxiolytic treatment may participate.)
[29] Having suicidal ideations detected by the Columbia Suicide Severity Rating Scale (C-SSRS), or attempted suicide in the past 15 years
[30] History of schizophrenia, bipolar disorder, or other severe mental illness
[31] Known history of alcohol or drug abuse or dependence (as defined by the DSM IV TR) within 5 years prior to enrolling
[32] Chronic hepatic diseases as indicated by liver function test abnormalities (At Visit 1, has alanine transaminase (ALT/SGPT) values >2 times the upper limit of normal (ULN) of the performing laboratory, aspartate transaminase (AST/SGOT) values >3 times the ULN, or total bilirubin values >2 times the ULN), or other manifestations of liver disease
[33] Has compromised renal function at Visit 1, as determined by creatinine clearance <30 mL/min based on Cockcroft Gault calculation of creatinine clearance
[34] History of unstable asthma, unstable chronic obstructive pulmonary disease, or other chronic respiratory conditions. (Note: Patients with stable disease, may participate.)

[35] Known positive human immunodeficiency virus (HIV) status, or history of syphilitic infection.
[36] A clinically significant abnormality in the 12 lead electrocardiogram (ECG), including complete heart block, bradycardia (heart rate <50 beats/minute), tachycardia (heart rate >=95 beats/minute), sinus pauses >2 seconds, second- or third-degree heart block, QTc >450 msec for males or QTc >470 msec for females. Note: patients with heart rate 45-50/beats/minute, and known history of bradycardia, and/or with history of extensive physical exercise in the past, or patients on adequate dose of beta-blockers could be included if the patient has no symptoms associated with 45-50/beats/minute heart rate.
[37] Treatment with an investigational small molecule with anti-amyloid properties within 1 year of study entry, or participation in a trial with an active or passive immunization against amyloid if patient was assigned to the active treatment arm;[38] Have any medical condition requiring treatment with warfarin, heparin or acenocoumarol
[39] Have any medical condition requiring double and triple anti-platelet treatment (for example, combination of aspirin with Clopidogrel, and/or Cilostazol). Note: single antiplatelet therapy is not an exclusion criterion.
[40] Are not capable of swallowing whole oral medications
[41] Fulfillment of any contraindications to a 1.5T or 3T MRI scan (for example, subjects with nonremovable ferromagnetic implants (such as cardiac pacemaker), aneurysm clips or other foreign bodies, or subjects with claustrophobic symptoms that would contraindicate an MRI scan)
[42] Sensitivity to florbetapir F 18
[43] Have allergy to all local anesthetics
[44] Are investigator-site personnel directly affiliated with the study, or are immediate family of the investigator site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
[45] Caregiver /study partner or patients that are Lilly employees

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-12-2012
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Florbetapir (18F)
Generic name:	-
Product type:	Medicine
Brand name:	LY2886721
Generic name:	-

Ethics review

Approved WMO Date:	19-06-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-08-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-10-2012
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-11-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-01-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-06-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-005217-37-NL
ClinicalTrials.gov	NCT01561430
CCMO	NL39540.056.12