A Phase III, Randomized, Placebo-Controlled, Parallel-Group, Double-Blind Clinical Trial to Study the Efficacy and Safety of MK-8931 (SCH 900931) in Subjects with Amnestic Mild Cognitive Impairment Due to Alzheimer*s Disease (Prodromal AD).

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To assess the efficacy of two doses of MK-8931 based on overall clinical progression in subjects with prodromal Alzheimer's Disease (AD).To assess the efficacy of two doses of MK-8931 in slowing clinical decline and disease progression in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Dementia and amnestic conditions
Study type	Interventional

Summary

ID

NL-OMON44848

Source
ToetsingOnline

Brief title
A Safety and Efficacy Study for Alzheimer's Disease (Prodromal AD)

Condition

- Dementia and amnestic conditions

Synonym
Alzheimer's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Sharp & Dohme (MSD) BV

Intervention

Keyword: Alzheimer, Prodromal

Outcome measures

Primary outcome

The primary efficacy endpoint is the change from Baseline in the CDR-SB score

at Week 104.

Secondary outcome

the time to progression to probable AD dementia

the mean difference between the last (Week 104) and first (Week 13) postdose

timepoint in CDR-SB

the change from Baseline at Week 104 in the CCS-3D

the change from Baseline at Week 104 in total hippocampal volume

the change from Baseline at Week 104 in CSF total tau

the change from Baseline at Week 104 in composite cortical amyloid standard

uptake value ratio assessed with amyloid tracer [18F]Flutemetamol using PET

imaging

the change from Baseline at Week 104 in ADCS-ADLMCI score

Study description

Background summary

Alzheimer*s disease (AD) is a slowly developing neurodegenerative disease that is the leading cause of dementia world-wide. Currently available treatments for AD are limited, and include acetylcholinesterase inhibitors (e.g., donepezil) and the low affinity N-methyl D-aspartate (NMDA) receptor antagonist (memantine). These medicines modestly improve symptoms but do not alter disease progression. Therefore, novel pharmacological agents that slow or halt the progression of AD are needed.
Alzheimer*s disease is characterized by specific histopathological features including amyloid deposits (plaques), neurofibrillary tangles, and neuronal degeneration. The *amyloid hypothesis* posits that amyloid * (A*) peptides aggregate into complexes, such as fibrils and plaques, which subsequently trigger the development of tau-related neurofibrillary tangles. These tangles are thought to be the more proximal cause of neuronal degeneration. A* pathology appears to begin years before the onset of AD dementia and is thought at some point to trigger tau pathology, neural degeneration, and the subsequent gradual emergence of clinical symptoms. As amyloid plaques continue to accumulate, tangle pathology spreads to a variety of brain regions, leading to progressive neuronal degeneration, brain atrophy, and cognitive decline. As a result, early intervention to reduce A* accumulation when patients are in the prodromal phase, or even earlier, has gained increasing acceptance as a promising approach to reduce the incidence of AD.
A* peptides are produced when amyloid precursor protein (APP) is cleaved by three distinct proteases: * secretase, BACE1 (* site APP cleaving enzyme 1, also known as *-secretase), and * secretase. Most APP is processed by * and * secretases to generate nonamyloidogenic peptides. However, 5-10% of APP is cleaved by BACE1 and * secretase to generate pathogenic A* peptides (A*40 and A*42). Deletion of BACE1 in mice eliminates A* in both the plasma and the brain. Thus, inhibition of BACE1 is a potential therapeutic strategy for slowing or halting progression of AD.
MK-8931 is a potent BACE1 inhibitor being developed for the treatment of AD. It has been shown to reduce A* levels in the CSF and brain of rodents and primates. MK-8931 also reduces A* in human CSF. In Phase 1 trials, MK-8931 has been generally safe and well tolerated (see IB). These results suggest that MK-8931 may reduce A* production in humans and could potentially slow

progression in subjects with prodromal AD. The disease modifying effects of MK-8931 in prodromal AD subjects will be evaluated with this protocol, which includes a two year treatment period and uses an outcome measure of overall disease severity.

Study objective

To assess the efficacy of two doses of MK-8931 based on overall clinical progression in subjects with prodromal Alzheimer's Disease (AD).

To assess the efficacy of two doses of MK-8931 in slowing clinical decline and disease progression in subjects with prodromal AD.

Study design

This is a double blind, randomized, parallel group, placebo controlled, multicenter trial in subjects with amnestic mild cognitive impairment (aMCI) due to Alzheimer's Disease (AD), referred to herein as prodromal AD. The trial includes two active dose arms of MK-8931 (12 mg and 40 mg) of MK-8931 and placebo. Duration of treatment is 104 weeks (24 months). MK-8931 is a potent * site APP cleaving enzyme 1 (BACE1) inhibitor being developed for the treatment of AD. The trial will enroll subjects who meet criteria for prodromal AD which is defined as subjects who have aMCI and are positive for an AD biomarker. The primary AD biomarker to be used for the inclusion criterion is cortical amyloid load measured with positron emission tomography (PET). Subjects who discontinue from trial treatment and are willing to return to the trial site should continue with scheduled visits as part of the retrieved drop out component of the study. Subjects who have completed the trial, demonstrated acceptable compliance with trial medication, and have not initiated acetylcholinesterase inhibitors or memantine during the trial will be eligible for enrollment in the separate extension protocol (if approved locally). In the extension study, all subjects who initially received placebo in the current protocol will receive active drug.
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.
This trial will use an independent, external Data Monitoring Committee (eDMC) to monitor safety and efficacy. There will be one formal interim analysis for futility as well as multiple interim reviews for safety. The formal interim futility analysis will be conducted when the first 50% of the total number of expected randomized PET positive subjects has had the opportunity to treat for 104 weeks.
Results of the interim analysis and safety reviews will be reviewed by the eDMC, which will make recommendations to the Sponsor to continue, modify or end the trial according to the eDMC charter and the plan described in Section 8.0-

Statistical Analysis Plan. The sponsor*s standing internal Data Monitoring Committee (siDMC), along with the eDMC, will determine when dosing may be initiated in the trial as described in Section 7.3.3.

Intervention

The study consists of two active dose arms of MK-8931 (12 mg and 40 mg), and placebo. One group will receive a once daily 12 mg tablet with product MK8931. One group will receive a once daily 40 mg tablet with product MK8931. The third group will receive a placebo tablet once daily.

Study burden and risks

Blood samples: drawing blood from your arm may cause pain, bruising, lightheadedness, and rarely, infection.

MRI: Risks of MRI include claustrophobia, discomfort due to lying still for a prolonged period of time, and other factors which will be described to you and discussed with you at the MRI center.

PET Imaging Scan: The risks of the PET scan include fear of small spaces, discomfort due to lying still for a long period of time, and other risks that the imaging study doctor will explain to you.

IV Line: When the PET tracer [18F]Flutemetamol is injected, you may feel a slight pin prick when the needle is inserted into your vein for the IV line. An IV line may cause faintness, swelling of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight chance of infection.

The electrocardiogram (ECG) procedure may cause minimal discomforts during the attachment and removal of the ECG leads to and from the skin.

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

Each subject must:;Added for the extension study:
Male/Female subjects who completed the initial 104-week trial.;For the main study:
* Be * 50 and * 85 years of age at the Screening Visit.;* Meet the following criteria for a diagnosis of prodromal AD:;o Each subject must report a history of subjective memory decline with gradual onset and slow progression for at least one year before Screening, that is either corroborated by an informant who knows the subject well or is documented in medical records.;o Each subject must have objective impairment in episodic memory at Screening that is *1.0 SD below the appropriate population mean as measured by the screening memory test [Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)]. An RBANS delayed memory index score of *85 is required for entry. (Note: the proportion of subjects with RBANS delayed memory index scores ranging from 79 to 85 (approximately 1.5 to 1.0 SD below the appropriate population mean), inclusive, will not exceed 15-30% of the total number randomized).;o Each subject must have general cognitive function and activities of daily living sufficiently intact, based on clinical assessment, so as not to meet criteria for mild AD dementia (based on DSM-IV-TR and NINCDS-ADRDA criteria).;o Each subject must have a positive amyloid imaging PET scan using [18F]flutametamol at Screening or positive CSF tau:A*42 ratio at Screening (see Trial Manuals for details). PET is the primary inclusion tool for the trial. Subjects who fail to meet inclusion criteria based on PET but qualify based on CSF will be enrolled in a separate CSF subgroup of the trial. (Refer to Protocol Section 7.1.3.4 for direction regarding initiation of CSF collection in the trial.);* Have an MMSE score * 24 at Screening.;* Be able to read at a 6th grade level or equivalent, as determined by the investigator, and must have a history of academic achievement and/or employment sufficient to exclude mental retardation.;* If receiving an acetylcholinesterase inhibitor, memantine, medical food/supplement, and/or herbal medications for AD, be on a stable dose for at least the three months before

Screening, and the subject must be willing to remain on the same dose for the duration of the trial. The treatment and dose that the subject is receiving at Screening must not be changed during the trial unless medically necessary. Additional treatments [including herbal medications] for AD that are not specified in the protocol must not be initiated during the trial. The subject and trial partner must agree that they do not plan to discontinue treatment or initiate additional AD treatments during the trial unless medically necessary. (See Protocol Section 5.5.2 for additional details regarding use of other AD therapy.);* Have a reliable and competent trial partner/informant who must have a close relationship with the subject, have face to face contact at least three days a week for a minimum of six waking hours a week, be willing to accompany the subject to all trial visits, and be willing to monitor compliance of the administration of the trial medication. The trial partner/informant should understand the nature of the trial and adhere to trial requirements (e.g., dose, visit schedules, receive phone calls, and evaluations).;* Have results of clinical laboratory tests (complete blood count [CBC], blood chemistries, thyroid stimulating hormone [TSH], and urinalysis) within normal limits or clinically acceptable to the investigator at Screening.;* Have results of a physical examination, vital signs, and ECG within normal limits or clinically acceptable to the investigator at Screening.

Exclusion criteria

The subject must be excluded from participating in the trial if the subject:;Added for the extension study:
1. Based on results from the EOT Visit (Visit 12) in the initial 104-week trial has results of clinical laboratory tests (complete blood count [CBC], blood chemi stries, and urinalysis) that are clinically unacceptable to the investigator.
2. Based on the results from the EOT Visit (Visit 12) has results of a physical examination, and vital signs that are clinically unacceptable to the investigator.;For the main study:
* Has a Rosen modified Hachinski Ischemia Score > 4 at Screening (i.e., evidence of vascular dementia).;* Has a known history of stroke or evidence from screening MRI scan that is clinically important in the investigator's opinion.;* Meets the criteria for a diagnosis of dementia, including probable or possible AD, based on DSM IV TR or NINCDS ADRDA criteria at Screening or Baseline.;* Has evidence of a clinically relevant neurological disorder other than the disease being studied (i.e., prodromal AD) at Screening, including but not limited to: vascular dementia, parkinsonism, frontotemporal dementia, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, progressive supranuclear palsy, neurosyphilis, dementia with Lewy bodies, other types of dementia, mental retardation, hypoxic cerebral damage, cognitive impairment due to other disorders, or head trauma with loss of consciousness that led to persistent cognitive deficits.;* Has evidence of a clinically relevant or unstable psychiatric disorder, based on DSM IV TR criteria, including schizophrenia or other psychotic disorder, bipolar disorder, major depression, or delirium. Major depression in remission is not exclusionary.;* Has evidence of a current episode of major depression based on investigator's judgment. A score on the 15-item Geriatric Depression Scale (GDS) of 5 or more requires an assessment by an appropriate health care professional to evaluate for the presence of major depression. Subjects with a score of 5 or

more who are not diagnosed with major depression following such an assessment may be included in the trial.;* Has an MRI scan obtained at Screening that shows evidence of a neurological disorder other than prodromal AD or > 4 cerebral microhemorrhages (regardless of their anatomical location or diagnostic characterization as "possible" or "definite"), a single area of superficial siderosis, evidence of a prior macrohemorrhage, > 3 lacunar infarcts over 10 mm each, any cortical infarct over 10 mm, or any other clinically significant finding (e.g., any lesion that may account for their cognitive impairment, including but not limited to brain tumor, severe white matter disease with a rating of 3 on the age-related white matter changes (ARWMC) scale, arteriovenous malformation, cavernous hemangioma, or any infarct in a strategic subcortical location).;* Has a history of hepatitis or liver disease that, in the opinion of the investigator, has been active within the six months prior Screening.;* Has a recent or ongoing, uncontrolled, clinically significant medical condition within three months of the Screening Visit (such as, but not limited to, diabetes, hypertension, thyroid or endocrine disease, congestive heart failure, angina, cardiac or gastrointestinal disease, dialysis, or abnormal renal function with estimated creatinine clearance < 30 mL/min) other than the condition being studied such that, in the judgment of the investigator, participation in the trial would pose a significant medical risk to the subject. Controlled co-morbid conditions (including diabetes, hypertension, heart disease, etc.) are not exclusionary if stable within three months of the Screening Visit. All concomitant medications, supplements, or other substances must be kept as stable as medically possible during the trial. Note: urinary tract infections at screening are not exclusionary if adequately treated (as documented by repeat urinalysis) prior to baseline.;* Has a history or current evidence of long QT syndrome, QTC interval * 470 milliseconds (for male subjects) or * 480 milliseconds (for female subjects), or torsades de pointes. (Note: Determination of QTc interval at Screening will be based on the average of three measurements, using the Fridericia formula for correction.);* Has a history of malignancy occurring within the five years immediately before Screening, except for a subject who has been adequately treated for ;o basal cell or squamous cell skin cancer, ;o in situ cervical cancer, or ;o localized prostate carcinoma; or ;o who has undergone potentially curative therapy with no evidence of recurrence for * 3 year post therapy, and who is deemed at low risk for recurrence by her/his treating physician.;* Has one of the following:;o clinically significant vitamin B12 or folate deficiency in the six months immediately before Screening, or;o vitamin B12 or folate deficiency in addition to increased serum homocysteine or methylmelonic acid levels at Screening as determined by central laboratory normal values.

Study design

Design

Study phase:	3
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):	27-08-2014
Enrollment:	33
Type:	Actual

Ethics review

Approved WMO Date:	01-11-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-01-2015
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-08-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	31-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-02-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-04-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	24-10-2017
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	EUCTR2012-005542-38-NL
CCMO	NL46287.056.13