A Randomized, Placebo Controlled, Parallel-Group, Double Blind Efficacy and Safety Trial of MK-8931 with a Long Term Double-Blind Extension in Subjects with Mild to Moderate Alzheimer*s Disease. (Protocol No. MK-8931-017) (also known as SCH 900931, P07738)

Published: 17-10-2012
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Part I:To assess the efficacy of two doses of MK-8931 on cognition in subjects with mild to moderate AD.To assess the efficacy of two doses of MK-8931 on functional ability in activities of daily living in subjects with mild to moderate AD.To assess...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON43729

Source
ToetsingOnline

Brief title
An Efficacy and Safety Trial of MK-8931 in Mild to Moderate AD (EPOCH)

Condition

- Other condition

Synonym
Mild to moderate Alzheimer's Disease

Health condition

neurologische aandoening

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Alzheimer's, EPOCH, Mild, Moderate

Outcome measures

Primary outcome

Part I: Primary Trial Objectives:

1. To assess the efficacy of two doses of MK-8931 on cognition in subjects with

mild to moderate AD.

2. To assess the efficacy of two doses of MK-8931 on functional ability in

activities of daily living in subjects

with mild to moderate AD.

3. To assess the safety and tolerability of three doses of MK-8931 in the

treatment of subjects with mild to

moderate AD.

Part II: Primary Extension Trial Objectives

1. To evaluate the safety and tolerability of MK-8931 in the long term

treatment of mild to moderate

Alzheimer*s Disease

2. To compare the efficacy of MK-8931 on cognition and functional ability in

activities of daily living in subjects

with mild to moderate AD in subjects administered MK-8931 for 24 months to that

of subjects administered

placebo for 18 months followed by MK-8931 for 6 months.

Secondary outcome

Part I: Secondary Trial Objective:

To assess the overall clinical response, as reflected by global assessment, of

two doses of MK-8931 in

subjects with mild to moderate AD.

Part II: Exploratory Extension Trial Objective:

To compare the efficacy of MK-8931 administered to subjects for 18 months to

that of subjects administered

placebo for 18 months in Part I followed by long term treatment of MK-8931 in

Part II on cognition, function,

disease progression, and health economic burden at multiple time points.

Study description

Background summary

Part I is a 78-week double blind, placebo controlled trial to evaluate the efficacy of *-site amyloid precursor protein (APP) cleaving enzyme (BACE) inhibitor MK-8931 as a potential disease-modifying therapy in subjects with mild to moderate AD. The trial is powered to detect a clinically significant change in the two coprimary
outcome measures (the Alzheimer*s Disease Assessment Scale Cognitive subscale

[ADAS-Cog] and the Alzheimer*s Disease Cooperative Study Activities of Daily Living Inventory [ADCS-ADL] change-from-baseline scores at Week 78).
At the end of the 78-week Treatment Period of Part I, subjects who have completed treatment may choose to participate in the extension trial (Part II), during which all subjects who received placebo in Part I will receive active drug. Part II will start with enrollment of the first subject who completes Part I and chooses to participate in the extension. Part II of the study will end when the drug either becomes commercially available or when the MK-8931 program is terminated. It is expected that Part II will have a duration of up to approximately 260 weeks (5 years) for the first subject enrolled.

Study objective

Part I:
To assess the efficacy of two doses of MK-8931 on cognition in subjects with mild to moderate AD.
To assess the efficacy of two doses of MK-8931 on functional ability in activities of daily living in subjects with mild to moderate AD.
To assess the safety and tolerability of three doses of MK-8931 in the treatment of subjects with mild to moderate AD.

Part II:
To evaluate the safety and tolerability of MK-8931 in the long term treatment of mild to moderate
Alzheimer*s Disease
To compare the efficacy of MK-8931 on cognition and functional ability in activities of daily living in subjects
with mild to moderate AD in subjects administered MK-8931 for 24 months to that of subjects administered
placebo for 18 months followed by MK-8931 for 6 months.

Study design

This study is comprised of two parts. Part I refers to the initial 78-week treatment period. Part II refers to the extension period (up to approximately 260 weeks) which will be available to subjects who complete Part I. Details for Part I are provided in Sections 5 to 8 of this protocol. Details for Part II are provided in Section 11 of this protocol.
Part I is a 78-week double blind, placebo controlled trial to evaluate the efficacy of *-site amyloid precursor protein (APP) cleaving enzyme (BACE) inhibitor MK-8931 as a potential disease-modifying therapy in subjects with mild to moderate AD. The trial is powered to detect a clinically significant change in the two coprimary outcome measures (the Alzheimer*s Disease Assessment Scale Cognitive subscale [ADAS-Cog] and the Alzheimer*s Disease Cooperative Study Activities of Daily Living Inventory [ADCS-ADL] change-from-baseline

scores at Week 78). At the end of the 78-week Treatment Period of Part I, subjects who have completed treatment may choose to participate in the extension trial (Part II), during which all subjects who received placebo in Part I will receive active drug. Part II will start with enrollment of the first subject who completes Part I and chooses to participate in the extension. Part II of the study will end when the drug either becomes commercially available or when the MK-8931 program is terminated. It is expected that Part II will have a duration of up to approximately 260 weeks (5 years) for the first subject enrolled.
Treatment Arms:
Part I: Initially, three dose arms and placebo will be included in the Safety Cohort. The 60 mg dose arm will not continue in the Main Cohort. Approval from the siDMC and eDMC is required for the 12 and 40 mg arms to continue in the Main Cohort; it is possible that the siDMC and eDMC could select only one dose, depending on the review of the safety data at the first formal interim safety analysis. If so, the sample size requirements will be updated as described in Section 8.2.9. For clarity and simplicity, the protocol is written assuming that the 12 and 40 mg dose arms will be included in the Main Cohort.
Part II: All active doses from Part I will be carried forward into Part II, with all subjects on active treatment continuing on their same treatment arm for Part II. Subjects originally on placebo will be assigned to the 40 mg dose. Sites and Subjects will remain blinded during Part II. The Sponsor will be unblinded following the completion of Part I.

Intervention

Investigational Product:
Part I :
- MK-8931 will be supplied as tablets of 12 mg, 40 mg and 60 mg. As assigned per the randomization,
subjects enrolled in the Safety Cohort will receive one of the following dosing regimens:
1. MK-8931 12 mg orally once daily (QD),
2. MK-8931 40 mg orally QD, or
3. MK-8931 60 mg orally QD.
Subjects enrolled in the Main Cohort will receive, per the randomization, either the 12 or 40 mg dose. Subjects
in the Safety Cohort who initially received the 60 mg dose prior to the first formal interim safety analysis will be
switched to the remaining higher dose for the remainder of the trial.

Reference Product: Matching placebo tablets: As assigned per the randomization, subjects will receive matching placebo tablets orally QD throughout the trial.

Part II:
MK-8931 will be supplied as tablets of 12 mg and 40 mg . All active doses from Part I will be carried forward

into Part II, with all subjects on active treatment continuing on their same treatment arm for Part II. Subjects
originally on placebo will be assigned to 40 mg:
1. MK-8931 12 mg orally once daily (QD)
2. MK-8931 40 mg orally once daily (QD)

Study burden and risks

Overall, the preclinical and clinical pharmacology suggests that MK-8931 may have a therapeutic effect in the treatment of AD and related disorders. Based on the preclinical and clinical safety data, specific guidance for the conduct of clinical trials
is recommended, namely to closely monitor vital signs (routine laboratory tests for liver function), cardiac rhythm, mental status changes (such as delirium), and dermatologic changes (such as rash and hair color). Regarding the potential for retinal and iris changes, a sub-study is included for patients in the lead-in Safety Cohort of the mild to moderate AD trial. These results will inform the need for additional monitoring in this and other trials. For pharmacogenetic testing, risks to the subject have been minimized.

Contacts

Public
Alzheimer Research Center

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part I Each subject must fulfill ALL the criteria listed below for entry
Each subject must be * 55 to * 85 years of age at the first visit.;Each subject must meet the criteria for a diagnosis of probable AD based on both a) the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer*s Disease and Related Disorders Association (NINCDS ADRDA) criteria and b) the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM IV TR) criteria for AD.;Each subject must have a Mini Mental State Examination (MMSE) score * 15 and * 26 at Screening.;Each subject must have a clear history of cognitive and functional decline over at least 1 year that is either a) documented in medical records or b) documented by history from an informant who knows the subject well.;Each subject must have a Magnetic Resonance Imaging (MRI) scan at the Screening Visit that is consistent with a diagnosis of AD.;Each subject must 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 a subject is receiving an acetylcholinesterase inhibitor, memantine, medical food/supplement (eg Vitamin E), and/or herbal medications for AD, the dose must have been stable for at least 3 months before Screening, and the subject must be willing to remain on the same dose for the duration of the trial. Subjects may need to be on AD treatments in accordance with local requirements. (The treatment and dose 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.);Each subject must have a trial partner who is reliable and competent. The trial partner must have a close relationship with the subject, have face to face contact at least 3 days/wk for a minimum of 6 waking hours/wk (or more in accordance with local requirements), 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 should understand the nature of the trial and adhere to trial requirements (eg, dose, visit schedules, and evaluations).;Each subject must 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.;Each subject must be willing to provide a blood sample for APOE and HLA genotyping.;Each subject must have results of a physical examination, vital signs, and electrocardiogram (ECG) within normal limits or clinically acceptable to the investigator at Screening.;Part II:
Each subject must have tolerated study medication and completed the initial 78-week period of the trial. Subjects who did not complete the initial 78 weeks of treatment may be permitted to continue in the extension at the discretion of the Sponsor.;Each subject must have a trial partner who is reliable and competent. The trial partner must have a close relationship with the subject, have face to face contact at least 3 days/wk for a minimum of 6

waking hours/wk (or more, based on local requirements), 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 should understand the nature of the trial and adhere to trial requirements (eg, dose, visit schedules, and evaluations). It is recommended that the trial partner accompany the subject to all trial visits.

Exclusion criteria

Part I:
A subject meeting any of the exclusion criteria listed below must be excluded from participating in the trial:
The subject has a Rosen-modified Hachinski Ischemia Score > 4 at Screening (ie, evidence of vascular dementia).
The subject has a known history of stroke or evidence from screening MRI scan that is clinically important in the investigator's opinion.
The subject has evidence of a clinically relevant neurological disorder other than the disease being studied (ie, probable 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, posterior cortical atrophy, logopenic primary progressive aphasia, 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.;The subject 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.;The subject has evidence of a current episode of major depression based on investigator's judgment. A score on the 15-item Geriatric Depression Scale 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.;The subject*s MRI scan obtained at Screening shows evidence of a neurological disorder other than probable 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, any cortical infarct over 10 mm, or any other clinically significant finding (eg, any lesion that may account for their cognitive impairment, including but not limited to brain tumor, severe white matter disease, arteriovenous malformation, cavernous hemangioma, or any infarct in a strategic subcortical location).;The subject has exudative (wet) age-related macular degeneration, active proliferative diabetic retinopathy, history of myopia or hyperopia > 8 diopters, pigment dispersion syndrome, pseudo-exfoliation syndrome, pigmentary glaucoma, glaucoma that requires > 2 classes of medications, intraocular pressure (IOP) > 21 mmHg (at the Screening Visit), clinically significant macula edema with diabetic retinopathy or advanced cataract to the degree that does not allow spectral-domain optical coherence tomography (SD-OCT) measurement, nystagmus, or other significant retinal diseases causing such significant distortion that baseline measurements would be too greatly abnormal to allow reasonable detection of

possible change.;The subject has a history of hepatitis or liver disease that, in the opinion of the investigator, has been active within the 6 months prior to Screening.;The subject has a recent or ongoing, uncontrolled, clinically significant medical condition within 3 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 comorbid conditions (including diabetes, hypertension, heart disease, etc) are not exclusionary, if stable within 3 months of the Screening Visit. All concomitant medications, supplements (eg Vitamin E),, or other substances
must be kept as stable as medically possible during the trial.;The subject 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.);The subject has a history of malignancy occurring within the 5 years immediately before Screening, except for a subject who has been adequately treated for ;1. basal cell or squamous cell skin cancer, ;2. in situ cervical cancer, or ;3. localized prostate carcinoma; or ;4. who has undergone potentially curative therapy with no evidence of recurrence for * 3 years post therapy, and who is deemed at low risk for recurrence by her/his treating physician.;The subject has;1. a history of clinically significant vitamin B12 or folate deficiency in the 6 months immediately before Screening, or;2. vitamin B12 or folate deficiency in addition to increased serum homocysteine or methylmelonic acid levels at Screening as determined by central laboratory normal values.;The subject has received any of the treatments listed in Table 1 of the protocol more recently than the indicated period before Screening. See Section 7.3.2.;Part II:
The subject is at imminent risk of self-harm, based on clinical interview or on the Columbia Suicidality Severity Rating Scale (C-SSRS), or of harm to others in the opinion of the investigator. Subjects must be excluded if they report suicidal ideation with intent, with or without a plan (ie, suicidal ideation Type 4 or 5 on the C-SSRS) in the past 1 month or suicidal behavior in the past 6 months.;The subject has developed a recent or ongoing, uncontrolled, clinically significant medical condition (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 Alzheimer*s disease 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. All concomitant medications, supplements (eg Vitamin E),, 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).;The subject has a history of, or has developed during Part I evidence of long QT syndrome, QTC interval * 470 milliseconds (for male subjects) or * 480 milliseconds (for female subjects), or torsades de pointes. ;The subject anticipates receiving any of the treatments listed in Table 13 of the protocol during the Part II.;The subject has developed a form of dementia that is not Alzheimer's disease, including but not limited to, dementia due to HIV infection, head trauma, vascular disease, Parkinson's disease, frontotemporal dementia, or Huntington's disease, as determined by the investigator.

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):	18-01-2013
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	17-10-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-12-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-01-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-07-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-02-2014
Application type:	Amendment
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:	07-04-2014
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-04-2014
Application type:	Amendment
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:	16-01-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-01-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2015
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:	06-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-08-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-09-2016
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	EUCTR2011-003151-20-NL
CCMO	NL41684.056.12
Other	nog niet bekend