A Phase 1 Double-blind, Placebo-controlled, Single- and Multiple-ascending-dose Study of KHK6640 in Alzheimer's Disease

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Primary objective: Single-ascending dose (SAD) and multiple-ascending dose (MAD) phases of the study: *To establish the safety and tolerability of single- and multiple-ascending dose(s) of KHK6640, respectively, in subjects with prodromal Alzheimer*...

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

Summary

ID

NL-OMON44211

Source
ToetsingOnline

Brief title
First-in-man safety study of KHK6640 in AD

Condition

- Mental impairment disorders

Synonym
Alzheimer's disease, Dementia

Research involving
Human

Sponsors and support

Primary sponsor: Kyowa Hakko

Source(s) of monetary or material Support: Kyowa Hakko Kirin Pharma;Inc. (Industry)

Intervention

Keyword: Alzheimer□s disease, Multiple-ascending dose, Single-ascending dose

Outcome measures

Primary outcome

Primary Parameters - Various routine safety assessments to assess safety

profile of KHK6640

Secondary outcome

Secondary Parameters:

Pharmacokinetic (PK) parameters include: Cmax, AUC0-t, R, AUC0-*, t1/2,

CL and Vss

* Immunogenicity: anti-KHK6640 antibodies

Study description

Background summary

This is the first study of KHK6640 to be conducted in humans. KHK6640 is an antibody that stops the toxic effects of amyloid beta, a protein that accumulates in the brains of people with AD and MCI/Prodromal AD. Amyloid beta protein has been shown to play an important role in the development of AD.

This study will test the safety, tolerability and potential effectiveness of different dose levels of KHK6640, given as a single dose and as multiple doseringen.

Study objective

Primary objective:
Single-ascending dose (SAD) and multiple-ascending dose (MAD) phases of the study:
*To establish the safety and tolerability of single- and multiple-ascending dose(s) of KHK6640, respectively, in subjects with prodromal Alzheimer*s

disease (AD) and mild-moderate AD; together hereafter referred to as AD in this synopsis.

Secondary objectives SAD and MAD phases of the study:
*To evaluate the pharmacokinetics (PK) of KHK6640 in serum;
*To evaluate the immunogenicity (anti-drug antibody) in serum;
*To determine the concentration of KHK6640 in cerebrospinal fluid (CSF).

Study design

This Phase 1, double-blind, placebo-controlled, dose-escalation study will enroll subjects with AD. This study is divided into two phases: a single ascending dose phase and a multiple ascending dose phase (SAD and MAD, respectively). Subjects in the SAD phase will have the option to continue to receive treatment in the MAD phase after completion of their SAD cohort and evaluation of up to 120 days of cumulative safety data for the same dose and the next higher dose cohort by the Safety Review Committee (SRC).

Please note that only cohort 1 SAD will start with sentinel dosing (first 4 patients).

Intervention

SAD Phase: Four (4) single-ascending intravenous (iv) dose cohorts of 10 subjects each will be evaluated: KHK6640 1, 3, 10, and 20 mg/kg, or placebo. Subjects will be randomized in an 8:2 ratio to receive a single dose of KHK6640 or placebo in the morning on Day 1 (Visit 1). All subjects will be kept for a 24-hour in-house confinement period on Day 1 to monitor for safety.

MAD Phase: Four (4) multiple-ascending iv dose cohorts of 10 subjects each will be evaluated: KHK6640 1, 3, 10, and 20 mg/kg or placebo. Subjects will be dosed at 28 day intervals for up to 5 in a cohort. A fifth cohort administered a sc dose of KHK6640 0.3 mg/kg or placebo may be evaluated (optional) by the Sponsor.

Study burden and risks

KHK6640 has not yet been tested in humans, so there is no clinical experience with administration of KHK6640, but since KHK6640 is a humanized (natural to humans) monoclonal antibody it is expected to have minimal risk of immune system hypersensitivity reactions, such as infusion reactions and immunogenicity (the body mounts an immune response to the drug). In the case of infusion reactions, some are allergic (anaphylactic) in nature and others are caused by the body*s releasedosesase of toxic substances, which can damage cells (anaphylactoid). In the case of immunogenicity there is a chance that KHK6640 could cause an acute allergic-type reaction.

Patients my experience additional discomforts during the following procedures as explained in the Informed consent:

Infusions: You may feel some discomfort from the study staff inserting an IV catheter (needle) into a vein in your arm. There is a risk of bruising, swelling and, on rare occasions, an infection may occur at the site where the needle was inserted. KHK6640 may leak out of your vein into the surrounding tissues creating diffusion or accumulation of the substance in the tissue.

Blood Tests: There may be some discomfort when blood samples are drawn, and there is a small risk of becoming light-headed. Bruising, swelling and, on rare occasions, an infection may occur at the site where the needle was inserted.

Electrocardiogram (ECG): This is a test that detects the electrical activity of the heart-beat and makes a picture of that activity. You may feel some discomfort when the electrodes are removed from your skin after the test.

Cognitive Skill level tests: The tests for mood and mental status may be slightly frustrating, produce fatigue and/or boredom.

Lumbar Puncture: There may be (temporary) pain. It is like taking a blood test, only it is in the back. You may also feel tingling sensation. On rare occasions you may experience headache, which is likely caused by a leaking of spinal fluid. If this headache doesn*t go away, you may be asked to drink fluids or it may require additional treatment, such as a patch called blood patch. A blood patch is an injection of some of your own blood into the lumbar puncture site to patch the spinal fluid leak. This is like plugging a leak in and it often helps to cure the headache immediately. Local anesthetic used prior to the lumbar puncture may cause allergic reaction. The symptoms of an allergic reaction after the injection of the local anesthetic include the following: excessive pain, redness or swelling near the injection site, body rash, wheezing and difficulty breathing. On very rare occasions you can experience vomiting, infection, temporary weakness of the eye muscle causing double vision, damage to nerves in your back, bleeding into the spinal fluid space, or death.

Magnetic Resonance Imaging (MRI) scan: the potential risk from MRI is that the machine attracts metal. If you have metal within your body (e.g., aneurysm clips or pacemakers), you will not be able to have this test done. Some people can feel *closed in* and get nervous (claustrophobia) or become uncomfortable with the loud noise when having an MRI scan in certain MRI scanners.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects with prodromal AD that is defined by Dubois criteria and mild to moderate AD that is defined by National Institute on Aging-Alzheimer's Association criteria will be enrolled in the study if they meet the following criteria:;1. Male or female subjects * 55 years of age at the time of enrollment;;2. CDR score of 0.5, 1.0, or 2.0;;3. Cognitive impairment episodic memory will be measured by the site using their preferred standard of measuring episodic memory;;4. CSF A* < 600 pg/mL and Tau > 300 pg/mL (by Innotest® enzyme-linked immunosorbent assay kit);;5. MMSE score > 16 at Screening;;6. Where symptomatic treatment of AD is clinically indicated, subjects must be on stable treatment (e.g., with an anticholinesterase inhibitor and/or memantine) for at least 12 weeks prior to the Screening visit;;7. Current antidepressant use must have been stable for at least 12 weeks prior to the Screening visit;;8. All other chronic use prescription medications must have been a stable dose for at least 4 weeks prior to the Screening visit;;9. Postmenopausal (defined as 12 months with no

menses without an alternative medical cause, and follicle stimulating hormone test) or surgically sterile women;;10. Sexually active male subjects of child-bearing potential (and their respective partners) must agree to use two medically accepted forms of effective contraception for the entire duration of the study and for 90 days after final administration of KHK6640, or the subject must be surgically sterile (with documentation in the subject's medical records);;11. Subjects (or subjects' legal guardians/permanent caregivers according to local requirements) who have given written informed consent.

Exclusion criteria

1. Subjects who previously received active treatment with an AD immunotherapy in an investigational study, with the exception of KHK6640 or placebo in the SAD phase;;2. Subjects who have been treated within 30 days before Screening (or 5 half-lives of the compound, if longer) with any investigational agents;;3. Subjects with a history of severe allergic, anaphylactic, or other hypersensitivity reactions, such as infusion reactions to chimeric, human, or humanized antibodies, or fusion proteins, or have known or suspected sensitivity to the investigational study drug or its excipients;;4. Subjects with a history of or presence of an active autoimmune disease and/or with an acute or chronic inflammation, and/or clinically relevant atopic condition;;5. Subjects with a history or presence of clinically significant seizures, brain trauma, transient ischemic attack, and/or cerebrovascular disease;;6. Subjects who meet National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS/AIREN) criteria for vascular dementia; ;7. Subjects with a presence of other neurodegenerative disease and/or psychiatric disorder (with the exception of successfully treated depression);;8. Subjects with any advanced, severe, progressive, or unstable disease that might interfere with the safety of the subject;;9. Subjects who have had a diagnosis of cancer or evidence of continued malignancy within 3 years of study enrollment (with the exception of adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, in situ breast cancer, or in situ prostate cancer with normal prostate-specific antigen [PSA] post resection);;10. Subjects who have renal, hepatic, cardiac, and/or other conditions that the Investigator considers would interfere with the study;;11. Subjects, who, for any reason, are judged by the Investigator to be inappropriate for this study, including a subject who is unable to communicate or to cooperate with the Investigator, who has/had a clinically significant illness or abnormal physical examination, psychiatric illness, disability, or social situation that may compromise the safety of the subject during the study or affect the ability of the subject to adhere to study procedures;;12. Subjects with the following hematological and chemistry laboratory values at Screening: White blood cell (WBC) count * 4000/mm3 or > 12000/mm3, Platelet count <100000/mm3, Calculated Creatinine Clearance (Cockcroft-Gault method) * 50mL/min, Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN), Total bilirubin 2 mg/dL, Hemoglobin (Hb) <11.0g/dL, Glycated serum hemoglobin A1c (HbA1c) * 9.0%, Diastolic blood pressure * 100 mmHg, QTc * 500 msec.;13. Subjects with a body weight <45 kg or > 120 kg;;14. Subjects who have a history of drug or alcohol abuse or dependence within the last year defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR);;15. Subjects who have any neurological condition that could be contributing to cognitive

impairment above and beyond that caused by the subjects' AD;;16. Subjects who have any psychiatric diagnosis (e.g., hallucinations, major depression, or delusions) that could interfere with assesment of cognition in the subjects;;17. Subjects who have evidence of infection, tumor, or other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening;;18. Subjects who have any conditions that would prohibit undergoing an MRI (e.g., presence of a cardiac pacemaker, or mental implants etc);;19. Subjects who have other significant pathological findings on brain MRI at Screening, including, but not limited to: more than four micro-hemorrhages, a single macro-hemorrhage, evidence of vasogenic edema, evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations or space-occupying lesions;;20. Subjects who require administration of a prohibited medication;;21. Subjects who have known HIV by serum titers;;22. Subjects who have known active hepatitis B based on polymerase chain reaction (PCR) testing for hepatitis B virus DNA. Subjects who are hepatitis B core antibody positive but PCR negative may be enrolled if placed on appropriate anti-hepatitis B virus prophylaxis. Subjects who are hepatitis B core antibody positive based on prior vaccination or because of previous illness need not receive prophylaxis. Subjects with known active hepatitis C by serum titers are also excluded.

Study design

Design

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):	02-10-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	KHK6640
Generic name:	N/A

Ethics review

Approved WMO Date:	03-04-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-06-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-06-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2016

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-08-2016
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	EUCTR2013-002873-23-NL
CCMO	NL48671.056.14