A Clinical Study of Two Doses of a Selective p38 MAP Kinase Inhibitor, VX-745, to Evaluate the Effects of 12-Week Oral Twice-Daily Dosing on Amyloid Plaque Load as Assessed by Quantitative Dynamic 11C-PiB Positive Emission Tomography (PET) Amyloid Scanning

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

Summary

ID

NL-OMON44613

Source
ToetsingOnline

Brief title
EIP-VX00-745-302

Condition

- Mental impairment disorders
- Dementia and amnestic conditions

Synonym

Alzheimer's disease, dementia

Research involving
Human

Sponsors and support

Primary sponsor: EIP Pharma, LLC
Source(s) of monetary or material Support: EIP Pharma;LLC

Intervention

Keyword: - Alzheimer's disease, - Amyloid plaque burden, - Quantitative dynamic 11C-PiB PET amyloid scanning, - Selective p38 MAP kinase inhibitor

Outcome measures

Primary outcome

The primary efficacy variables are:

* Change from Baseline to Week 12 within each treatment group in quantitative relative cortical uptake of 11C-PiB as assessed by dynamic PET scanning at baseline and at end of treatment

* Number and proportion of responders by quantitative dynamic PET scanning within each dose group (response defined as *7% reduction in amyloid plaque load)

Secondary outcome

The secondary efficacy variables are change from Baseline to Week 12 in Mini-Mental State Examination (MMSE), and Wechsler Memory Scale (WMS). No change in cognitive score is anticipated during the brief 12-week period of treatment. Nevertheless, the cognitive assessment will be conducted to determine whether any improvement is observed, and as part of the safety assessment to ensure that there is no marked deterioration of performance.

In addition, MEG and resting state fMRI data will be obtained in order evaluate for a signal of activity on synaptic function, and to obtain initial treatment effect data to design/size future studies in which one of these measures would be a primary efficacy measure.

Other endpoints are pharmacokinetics and safety.

Study description

Background summary

Alzheimer*s disease (AD) is a progressive brain disease that results in impaired cognitive function, such as memory and thinking, and ultimately impairs one*s ability to complete simple daily tasks. Available treatments provide symptomatic relief for a period of time, but do not prevent or slow neuronal loss and inevitable disease progression. The importance of microglia-driven inflammation in the central nervous system of human Alzheimer's disease, and the role of p38 MAPK in regulating microglia, have recently been defined. VX-745 binds to the ATP binding pocket of p38 MAPK and inhibits the kinase competitively. VX-745 nonclinical data suggest that it may have a therapeutic effect in patients with inflammatory diseases of both the peripheral and central nervous systems.

Study objective

The primary objective is to assess the effects on amyloid plaque burden of administration of VX-745 for 12-weeks, as assessed by Dynamic 11C-PiB (Carbon-11 labeled Pittsburgh Compound B) PET Amyloid Scanning in patients with Mild Cogntitive Impairment due to Alzheimer*s Disease (*MCI due to AD*) or mild Alzheimer*s disease (AD).

The secondary objectives are:
- To develop a PK/PD model for VX 745 and amyloid plaque burden reduction, if an effect on amyloid plaque burden is observed.
- To obtain a preliminary evaluation of the safety and tolerability of VX-745 in patients with MCI or AD.
- To obtain data on the effects of VX-745 on synaptic function as assessed by Magnetoencephalography (MEG) and resting state functional Magnetic Resonance

Imaging (fMRI).

Study design

This is a phase IIa, monocenter, multiple-dose, open-label study of VX-745 (40 mg or 125 mg) administered twice daily for 12 weeks in subjects with a confirmed diagnosis of MCI or AD.

Intervention

Once eligibility is confirmed and before the first dose of VX-745, subjects will be randomly assigned to one of two VX-745 dose groups. Investigators and patients will be blind to the dosage strength. Dosing will start on Day 1 following completion of all Baseline procedures. During the treatment period, subjects will return to the clinic on Days 14, 28, 56, and 84. A Follow-up visit will be conducted 14 (±3) days following the last dose of VX-745. Dynamic PET scanning with full quantitative analysis will be performed at baseline and at the end of treatment.

Study burden and risks

Based on the nonclinical and clinical data available to date and the planned safety monitoring, the overall risk-benefit balance for this trial is considered to be acceptable.

Foreseeable benefits

The current study represents the first clinical investigation in Alzheimer's disease of VX-745. Available treatments provide symptomatic relief for a period of time, but do not prevent or slow neuronal loss and inevitable disease progression. VX-745 nonclinical data suggest that it may have a therapeutic effect in patients with inflammatory diseases of both the peripheral and central nervous systems.

Possible side effects of the study drug

The medicinal product being studied is called VX-745. This study may cause the following side effects:
- headache
- common cold
- gastroenteritis (inflammation of the stomach and the small intestine)
- diarrhea
- dizziness
- sleeplessness/ insomnia
- dyspnea (breathlessness)
- myalgia (muscle pain)

- abdominal pain
- elevations in liver enzymes, markers of potential injury to the liver
- reduction of fever and inflammation, which may mask the signs of infection
- pharyngitis (inflammation of the throat) and rhinitis (inflammation of the mucous membrane inside the nose).

Known risks of study procedures
* Blood samples: it can be painful when blood is taken. Some people become dizzy or faint when blood is collected. Some may also develop an infection (rare), bleeding, redness or bruising at the site at which the blood is taken.
* ECG: the plasters that are used can cause skin irritation.
* MEG: there are very few know risks of MEG (magnetoencephalography). Sitting inside the machine can feel constraining or frightening to someone who is prone to such feelings, but unlike a MRI machine a MEG machine is not built as a tunnel and this risk is rare. There are is also a theoretical risk of leakage of the fluid that is used to cool the magnets inside the machine, but there are safeguards built into the machine to prevent injury.
* PET scan: subjects will be exposed to a small amount of radioactivity from the tracer for the PET scan. The risk of the radiation dose from this study is considered small. Although this radiation dose is considered to be acceptable by current guidelines, the effect of radiation adds up over the lifetime. Any increase in the amount of radiation received above natural background radiation carries with it a risk of later developing serious and possibly fatal conditions, including cancer. It is also possible, although very unlikely, to have an allergic reaction to the radioactive substance used for this scan. Some people have pain, redness, or swelling at the injection site.
* MRI scan: there are no known side effects of exposure to the powerful magnetic field used by MRI scanners. There are strict safety regulations in place before an MRI scan is performed.

Risks to the unborn child
If the patient is a man with a female partner who can become pregnant, he will be asked to use at least one of the following contraceptive methods from before first dose on Day 1 through 7 days following the last dose of study drug: complete abstinence, sterilization, or condom use.

A woman cannot be in this study if she is pregnant, planning to become pregnant during the study or nursing a child. If the patient is a woman and can still become pregnant, she will be asked to use at least one of the following contraceptive methods from before first dose on Day 1 through 7 days following the last dose of study drug: complete abstinence, birth control pill (or contraceptive injection), intrauterine device, or condom use.

Risk from radiation
X-rays or radiation from radioactive materials can damage genes. This damage of genes can lead to cancer or a congenital defect. In the above mentioned radiation, there will be no other side effects of radiation than redness of the

skin or hair loss.

For further information about risks and side effects, please refer to the patient information leaflet.

Patients will be monitored for safety throughout the study. Unforeseen/unwanted events will be taken care of by the study staff at all sites, which are experienced in handling patients with AD and in conducting similar clinical trials.

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

1. Men and women age 60-85 years.;2. Willing and able to provide informed consent.;3.

Confirmed diagnosis of mild cognitive impairment due to Alzheimer*s disease (MCI due to AD) or mild AD.;4. Mini-Mental State Examination (MMSE) score ranging from 20 to 28, inclusive.;5. Evidence of amyloid pathology by Amyloid PET scan determined by visual inspection (any method) by an experienced nuclear medicine physician.;6. If the patient is taking drug for AD (e.g.; donepezil or memantine), he has been on a stable dose for at least 3 months.;7. Dutch-speaking.;8. Adequate visual and auditory abilities to perform all aspects of the cognitive and functional assessments

Exclusion criteria

1. Evidence of neurodegenerative disease other than AD (including but not limited to vascular dementia, dementia with Lewy bodies, and Parkinson*s disease).;2. Subject has any concurrent medical or psychiatric condition that, in the opinion of the investigator, would compromise his/her ability to comply with the study requirements.;3. History of cancer within the last 5 years, except basal cell carcinoma, non-squamous skin carcinoma, prostate cancer or carcinoma in situ with no significant progression over the past 2 years.;4. Significant cardiovascular, pulmonary, renal, liver, infectious disease, immune disorder, or metabolic/endocrine disorders or other disease that would preclude treatment with p38 MAP kinase inhibitor and/or assessment of drug safety and efficacy.;5. History of an allergic reaction of any severity to 11PiB injection.;6. Subject participated in a study of an investigational drug less than 3 months or 5 half-lives of the investigation drug, whichever is longer, before enrollment in this study.;7. Male subjects with female partners of child-bearing potential who are unwilling or unable to adhere to contraception requirements.;8. Female subjects who have not reached menopause or have not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy.;9. Positive urine or serum pregnancy test or plans or desires to become pregnant during the course of the trial.;10. Contraindications (e.g. pacemaker, vascular stent or stent graft) to MRI testing.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-05-2015
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not available
Generic name:	not available

Ethics review

Approved WMO Date:	11-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2014-002855-25-NL
CCMO	NL50211.029.14