A Double-Blind, Placebo-Controlled Proof-of-Concept Study of a Selective p38 MAP Kinase Alpha Inhibitor, Neflamapimod, Administered for 24 Weeks in Subjects with Mild Alzheimer*s Disease.

Published: 21-02-2018
Last updated: 10-04-2024

The primary objective is to evaluate the effects of administration of neflamapimod (VX-745) for 24-weeks on immediate and delayed recall aspects of episodic memory, as assessed by the Hopkins Verbal Learning Test * Revised (HVLT-R) in subjects with...

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

Summary

ID

NL-OMON48874

Source
ToetsingOnline

Brief title
proof-of-concept research with a nephlamapimod in Alzheimer's disease

Condition

- Mental impairment disorders
- Dementia and amnestic conditions

Synonym
Mild Alzheimer□s Disease

Research involving
Human

Sponsors and support

Primary sponsor: WORLDWIDE CLINICAL TRIALS d.o.o.
Source(s) of monetary or material Support: EIP Pharma LLC

Intervention

Keyword: Double-Blind, Mild Alzheimer□s Disease, Neflamapimod, Proof-of-Concept Study

Outcome measures

Primary outcome

Primary efficacy endpoints:

* Combined change in z-scores of total recall and delayed recall on the HVLT-R

in neflamapimod-treated subjects compared to placebo-recipients.

Secondary outcome

Secondary endpoints:

* Change in WMS immediate and delayed recall composites in neflamapimod-treated

subjects compared to placebo-recipients.

* Change in CDR-SB in neflamapimod-treated subjects compared to

placebo-recipients.

* Change in MMSE in neflamapimod-treated subjects compared to

placebo-recipients.

* Change in CSF biomarkers (total tau, p-tauR181R, A*R1-40R, A*R1-42,

neurogranin Rneurofilament light chain) in neflamapimod-treated subjects

compared to placebo-recipients.

Study description

Background summary

Based on the clinical experience to date at higher doses and the results from animal toxicology studies, the neflamapimod dose of 40 mg BID and lower is expected to be well tolerated and to have a low risk of drug toxicity.

With the consistent effect on recall component of episodic memory across the 2 studies, and corroboration using 2 different assessment tools in distinct patient populations, the phase 2a clinical data provide preliminary evidence that neflamapimod is pharmacologically active in a manner that is consistent with the scientific rationale and preclinical data that indicate the potential to reverse synaptic dysfunction in the hippocampus. The objective of the current study then is to demonstrate proof-of-concept for neflamapimod by replicating the phase 2a results of improving episodic memory function in a placebo-controlled study. In addition, a general clinical measure of cognition and function (Clinical Dementia Rating Scale [CDR]) will be assessed both to determine whether there is evidence of improvement and estimating potential treatment effects to support Phase 3 study design

Study objective

The primary objective is to evaluate the effects of administration of neflamapimod (VX-745) for 24-weeks on immediate and delayed recall aspects of episodic memory, as assessed by the Hopkins Verbal Learning Test * Revised (HVLT-R) in subjects with mild Alzheimer*s disease (AD).

Study design

This is a Phase 2, multicenter, randomized, double-blind, placebo- controlled, proof-of-concept study of neflamapimod 40 mg or matching placebo administered twice daily for 24 weeks in subjects with mild AD.
Following completion of informed consent procedures, subjects will enter the Screening phase of the study.
Two Screening visits are planned to allow most screening procedures to be completed and reviewed during the first visit before lumbar puncture to collect CSF is performed during Screening Visit 2.
Once eligibility is confirmed and before the first dose of study drug, subjects will be randomly assigned on 1:1 basis to placebo or neflamapimod treatment.
Investigators and subjects will be blinded to the treatment assignment.
Dosing will start on Day 1 following completion of all Baseline procedures.
During the treatment period, subjects will return to the clinic on Days 21, 42, 84, 126, and 168.
Episodic memory and other cognitive assessments will be performed at Baseline and Days 42, 84, and 168.
Lumbar puncture will be performed, and CSF collected at Screening Visit 2 and on Day 168.
A Follow-up visit will be conducted 14 (±3) days following the last dose of study drug.

Intervention

Once eligibility is confirmed and before the first dose of study drug, subjects will be randomly assigned on 1:1 basis to placebo or neflamapimod treatment. Investigators and subjects will be blinded to the treatment assignment.

Study burden and risks

Side Effects of Neflamapimod
To date, approximately 175 subjects have received neflamapimod at dose up to 750 mg twice a day, and for up to 3 months. As such, all of its possible side effects may not be known.
In clinical studies prior to those conducted in subjects with AD, headache, common cold, gastroenteritis, diarrhea, and sleeplessness/ insomnia have been the most common adverse events reported. Gastroenteritis and diarrhea, which have been primarily mild, appear to have the strongest association with neflamapimod treatment.
25 subjects with Alzheimer's disease have been dosed in 2 different studies with different treatment durations (6 or 12 weeks) where neflamapimod doses of 40 and 125 mg twice a day were studied. Excluding 1 subject who discontinued early, all other subjects completed their scheduled dosing period.
The possible side effects seen in these 2 studies that you may develop included:
* feel sleepy or drowsy
* loose stools
* vomiting
In a previous study in subjects with rheumatoid arthritis who received a dose of neflamapimod that is 5 times higher than the dose you will be receiving, approximately 1 in 7 patients developed abnormalities in blood tests of liver function. Though such liver function test abnormalities were not seen at the doses utilized in the AD studies.

Risks to an Unborn Child
Women
Currently there is no information in humans on this study drug with respect to pregnancy and breast-feeding.

Men
Neflamapimod may harm an unborn child.

Unknown Risks
There may be risks to you that are currently not known or cannot be predicted.

Placebo Risks
If the subject are in the group that is assigned to placebo (the medically inactive substance), there symptoms of indication may not improve or may even worsen.

Allergic Reactions
As with taking any drug, there is a risk of allergic reaction. If the subject has a very serious allergic reaction, they may be at risk of death. Some symptoms of allergic reactions include an itchy rash (hives) or swelling of the throat making it difficult to breathe.

Blood Sampling
The risks of taking blood include fainting and pain, bruising, swelling, or rarely infection where the needle was inserted. These discomforts are brief and transient.
The total volume to be collected during your 24-week participation in this research study is 74.5 mL (ie, 5 tablespoons).

Lumbar Puncture:
LP (also called spinal tap) involves insertion of a needle into the spinal canal to collect spinal fluid for testing. In most cases, the patient is asked to sit and bend forward or lay down on an examination table, and the spinal needle is inserted after a numbing agent is applied to the skin at the lower back. For most people, a lumbar puncture does not cause any serious problem; the most common side effect is headache. In rare cases, if the headache does not go away in couple of days, it may be due to spinal fluid leak from the puncture site. This can be treated with a *blood patch* (a small amount of your blood injected into the puncture site). Less common side effects include pain at the place where the needle was inserted, back, neck, or shoulder pain; these can be treated and usually improve over time. Other complications such as low blood pressure, dizziness, bleeding into the spinal canal, or an infection of the spinal fluid are very uncommon, and may require treatment in the hospital.

Electrocardiogram
Skin irritation from the ECG electrode pads or pain when removing the pads are possible side effects.

Contacts

Public
WORLDWIDE CLINICAL TRIALS d.o.o.

Ulica grada Vukovara 284 Zagreb
Zagreb 10000
HR
Scientific
WORLDWIDE CLINICAL TRIALS d.o.o.

Ulica grada Vukovara 284 Zagreb
Zagreb 10000
HR

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 55 to 85 years, inclusive.
2. Willing and able to provide informed consent.
3. Must have mild cognitive impairment (MCI) or mild AD with evidence of progression (*Mild-AD*), as defined by the following:
a. CDR-Global Score of 0.5 or 1.0, with CDR memory subscore of at least 0.5.
b. MMSE score ranging from 20 to 28, inclusive.
c. Positive biomarker for AD, as defined by a CSF A*1-42 below the threshold and phospho-tau above the threshold for the assay utilized in the study and assessed by the central laboratory.
4. Computed tomography (CT) or magnetic resonance imaging (MRI) findings within 2 years of Screening that are compatible with AD (i.e. no other pathologic processes that would potentially account for the cognitive deficit)
5. If the patient is taking a single drug for AD (e.g., donepezil or other cholinesterase inhibitors or memantine; dual therapy is excluded), he/she has been on a stable dose for at least 2 months prior to baseline, and the dose must remain unchanged during the study unless required for management of adverse events (AEs).
6. Adequate visual and auditory abilities to perform all aspects of the cognitive and functional assessments.
7. Must have reliable informant or caregiver. In Czech Republic only, the caregiver must be either sharing the same household as the subject or be in personal contact with the subject at least 5 days per week.

Exclusion criteria

1. Evidence that the primary basis for cognitive impairment is neurodegenerative disease other than AD, including, but not limited to, vascular dementia, dementia with Lewy bodies, and Parkinson*s disease.;2. Suicidality, defined as active suicidal thoughts within 6 months before Screening or at Baseline, defined as answering yes to items 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS), or history of suicide attempt in previous 2 years, or, in the Investigator*s opinion, at serious risk of suicide.;3. History of major and active psychiatric disorder, moderate to severe depressive symptoms, and or other concurrent medical condition that,in the opinion of the Investigator, might compromise safety and/or compliance with study requirements.;4. Diagnosis of alcohol or drug abuse within the previous 2 years.;5. History of cancer within the last 5 years, except basal cell carcinoma, squamous skin carcinoma, prostate cancer or carcinoma in situ with no significant progression over the past 2 years.;6.Poorly controlled clinically significant medical illness, such as hypertension (blood pressure > 180 mmHg systolic or 100 mmHg diastolic; myocardial infarction within 6 months; uncompensated congestive heart failure or other significant cardiovascular, pulmonary, renal, liver, infectious disease, immune disorder, or metabolic/endocrine disorders or other disease that would preclude treatment with p38 mitogen activated protein (MAP) kinase inhibitor and/or assessment of drug safety and efficacy.;7. History of serum B12 abnormality, anemia with hemoglobin *10 g/dL, thyroid function abnormality, electrolyte abnormality, or positive syphilis serology that have not been corrected and/or otherwise addressed.;8.History of epilepsy or unexplained seizure within the past 5 years.;9. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio (INR) >1.5;10. Known human immunodeficiency virus, or active hepatitis B, or active hepatitis C virus infection.;11. 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.;12. Male subjects with female partners of child-bearing potential who are unwilling or unable to adhere to contraception requirements specified in the protocol.;13. Female subjects who have not reached menopause or have not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy.;* If a female subject reached menopause within the previous year, a pregnancy test must be performed during Screening and the subject must be willing to adhere to the contraception requirements specified in the protocol;14. Requires concomitant use of strong cytochrome P450 (CYP) 3A4 inhibitors or anti-tumor necrosis factor-alpha therapies during study participation.
Such subjects with a positive urine or serum pregnancy test are not eligible for study participation.

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):	14-05-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Neflamapimod
Generic name:	neflamapimod

Ethics review

Approved WMO Date:	21-02-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-06-2018
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	11-03-2019
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	EUCTR2017-004388-11-NL
CCMO	NL64424.056.18