A Double-Blind, Placebo-Controlled 16-Week Study of the Cognitive Effects of the Oral P38 Alpha Kinase Inhibitor Neflamapimod in Dementia with Lewy Bodies (DLB)

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

Summary

ID

NL-OMON49197

Source
ToetsingOnline

Brief title
A Study of Neflamapimod in Subjects with DLB.

Condition

- Other condition
- Dementia and amnestic conditions

Synonym
dementia, neurodegenerative disease

Health condition

Dementia with Lewy Bodies (DLB)

Research involving
Human

Sponsors and support

Primary sponsor: EIP Pharma Inc.
Source(s) of monetary or material Support: EIP Pharma Inc.

Intervention

Keyword: Study of Neflamapimod in DLB.

Outcome measures

Primary outcome

Primary endpoints:

*Change in the composite score of the NTB, including assessments of attention, executive function, and visuospatial function in neflamapimod treated-subjects as compared to the placebo-treated subjects.

Secondary outcome

Secondary endpoints:

*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 NPI-10 domains in neflamapimod-treated subjects compared to placebo-recipients.

*Change in International Shopping List Test immediate & delayed recall and recognition in neflamapimod-treated subjects compared to placebo-recipients.

*Change in Timed Up and Go Test.

*Change in EEG parameters.

Study description

Background summary

This is a double-blind, placebo controlled research study to compare any levels of improvement in memory and attention in patients with mild to moderate DLB after taking neflamapimod or placebo.

Patient will receive the study drug (neflamapimod or placebo) in the form of capsules and will take them by mouth with food, twice a day if weigh less than 80 kg (176 lb) or 3 times a day if weigh 80 kg (176 lb) or more. The study duration is 16 weeks.

The purpose of this study is to investigate how safe and effective the new medicine neflamapimod is when it is administered to patients with Dementia with Lewy Bodies (DLB). Doctors cannot prescribe neflamapimod yet outside of a study. The efficacy of neflamapimod will be compared to the efficacy of a placebo.

The purpose of this study is to determine whether neflamapimod can improve learning skills, problem solving skills, and memory loss in people diagnosed with mild to moderate DLB. More specifically, the aim of this study is to find out if you experience any improvement in your:
* Verbal learning, memory, and attention
* Cognitive and functional performance
In this research study, a new drug named neflamapimod will be tested for the treatment of mild to moderate DLB. In other words, neflamapimod is not sold as a drug yet in the US as it has not yet been approved for marketing by the US Food and Drug Administration (FDA). Neflamapimod is an experimental drug; *experimental* means that its efficacy has not yet been confirmed by clinical trials in DLB, and therefore it has not been approved by the US FDA or European Medicines Agency (EMA) or any other regulatory agency. This Phase 2 study is being conducted for research purposes only and is required for a possible marketing approval of neflamapimod by the regulatory agencies (like the FDA) around the world.

Study objective

The primary objective is to evaluate the effect of neflamapimod on cognitive function as assessed in a study-specific Neuropsychological Test Battery (NTB) comprised of:
*Cogstate Detection test (DET)
*Cogstate Identification test (IDN)

*Cogstate One Card Learning test (OCL)
*Cogstate One Back test (ONB)
*Letter Fluency Test
*Category Fluency Test (CFT)

The secondary objectives are to:
*Evaluate the effects of neflamapimod on informant/caretaker evaluation of cognition and function, as assessed by the Clinical Dementia Rating Scale-sum of Boxes (CDR-SB).
*Assess the effects of neflamapimod on general cognition, as assessed by the Mini Mental State Examination (MMSE).
*Assess the effects of neflamapimod on episodic memory, as assessed by the International Shopping List Test (ISLT).
*Assess the effects of neflamapimod on select domains of the 10-item Neuropsychiatric Inventory (NPI-10), including depression (dysphoria), anxiety, hallucinations, and agitation/aggression.
*Evaluate the effects of neflamapimod on motor function as assessed by the Timed Up and Go Test (TUG).
*Evaluate the effects of neflamapimod on quantitative electroencephalography (EEG) parameters.

Study design

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, proof-of-principle study of neflamapimod versus matching placebo (randomized 1:1) administered with food for 16 weeks in subjects with DLB. Subjects weighing <80 kg will receive 2 capsules per day (in divided doses) and those weighing *80 kg will receive 3 capsules per day (in divided doses). Subjects receiving two capsules per day will be administered 1 capsule, twice daily (BID) with food (i.e., with the morning and evening meals), either neflamapimod 40 mg or placebo. Subjects receiving 3 capsules per day will be administered 1 capsule three times daily (TID) with food (i.e., with the morning, mid-day, and evening meals), either neflamapimod 40 mg or placebo. Doses should be administered at least 3 hours apart.
Following completion of informed consent procedures, subjects will enter the Screening phase of the study.
One to two Screening visits are planned, during which safety screening measures will be undertaken, a practice NTB will be performed, and the required diagnosis and cognitive impairment will be confirmed. Screening will be conducted within 21 days before Baseline (Day 1). If a DaTscan* is required to determine study eligibility, Screening may be extended to 35 days.
Once eligibility is confirmed and before the first dose of study drug, subjects will be randomly assigned on a 1:1 basis to placebo or neflamapimod for the 16-week treatment period. Investigators and subjects will be blinded to the treatment assignment. Randomized subjects will be stratified by International Shopping List Test (ISLT) Total Recall score at Baseline (< 21 vs. >21), i.e. by wheter patients have an episodic memory defect at baseline or not.

Subjects will receive study drug for 16 weeks. Dosing will start on Day 1 following completion of all baseline procedures. During the 16-week treatment period, subjects will return to the clinic every 2 weeks for the first month and then every 4 weeks thereafter. A Final Study Visit (i.e. Follow-Up Visit) will be conducted 2 weeks (+/-3 days) after completion of study drug or after the Early Termination (ET) visit.
The NTB, ISLT, and NPI-10 will be conducted at Screening, Baseline (Day 1), Week 4 (Day 28), Week 8 (Day 56), and Week 16 (Day 112) or ET if early termination. The CDR-SB and TUG will be conducted at Baseline (Day 1), Week 8 (Day 56), and Week 16 (Day 112) or ET. The MMSE will be conducted at Screening, Baseline (Day 1), Week 8 (Day 56), and Week 16 (Day 112) or ET. EEGs will be conducted at Baseline (Day 1) and Week 16 (Day 112) or ET. Samples for plasma biomarkers will be obtained at Screening, Baseline (Day 1) and Week 16 (Day 112) or ET.

Intervention

Once eligibility is confirmed and before the first dose of study drug, subjects will be randomly assigned on a 1:1 basis to placebo or neflamapimod for the 16-week treatment period. Investigators and subjects will be blinded to the treatment assignment. Randomized subjects will be stratified by International Shopping List Test (ISLT) Total Recall score at Baseline (< 21 vs. >21), i.e. by wheter patients have an episodic memory defect at baseline or not.

Study burden and risks

Possible side effects of Neflamapimod
Neflamapimod may cause side effects.

To date, approximately 270 subjects have received neflamapimod at doses up to 750 mg twice a day, and for up to 6 months.
103 subjects with Alzheimer's disease were dosed in 3 different studies with different treatment durations (up to 24 weeks) where neflamapimod doses of 40 and 125 mg twice a day were studied. Overall neflamapimod was well-tolerated with 3 subjects who discontinued early, all other subjects completed their scheduled dosing period.
The most common side effects seen in these 3 studies included:

* diarrhea (8%)
* headache (7%)
* sleepiness (5%)
* falling (5%)

This is the first study testing neflamapimod in patients with DLB. Even if you are in the group that gets the active drug (neflamapimod, the medically active substance) during the study, your DLB-related symptoms may not improve or may

worsen.
In clinical studies prior to those conducted in subjects with Alzheimer*s disease, headache, common cold, gastroenteritis (nausea/vomiting), diarrhea, and sleeplessness/insomnia have been the most common adverse events reported. Nausea/vomiting and diarrhea, which have been primarily mold, appear to have the strongest association with neflamapimod treatment.
In addition, abnormalities in blood tests of liver function have been seen in subjects treated with neflamapimod. Elevations to 3 times the normal range was seen in 1 of 95 subjects with earlyAlzheimer*s disease at doses of 40 mg twice a day, and in 1 of 7 subjects with rheumatoid arthritis treated at a dose of 250 mg twice a day. You will have periodic blood tests during the study to monitor liver function.

Neflamapimod, the study medicine may also have adverse effects/side effects that are still unknown.

Risks to an Unborn child
The consequences of this study drug for an unborn child are not known.

Tests
Blood sampling
Drawing blood may be painful or cause some bruising.
The risks of taking blood include fainting as well as pain, bruising, swelling, or infection where the needle was inserted. These discomforts are brief and usually do not last long.

Placebo Risks
The DLB symptoms may not improve or may even worsen.

Allergic Reactions
As with taking any drug, there is a risk of allergic reaction. This reaction can be mild, such as rash or hives, but also severe, such as breathing problems due to swelling of the throat or shock, even risk of death.

DaTscan*
When a DaTscan* is performed, patient is exposed to radiation because of both the Ioflupane I 123 chemical and the procedure. A DaTscan* can also cause headache, nausea, vertigo, dry mouth, or dizziness. These reactions are usually mild to moderate. In addition, reactions to the chemical injection, usually redness of the skin, itching, and pain at the injection site, have been reported. The chemicals from a DaTscan* are excreted into human milk; therefore if patient is nursing a child it is recommended to interrupt nursing and pumping and discarding breast milk for 6 days after the DaTscan*. If patient is taking drugs that bind to a dopamine transporter, this may interfere with the scan images.
The total amount of radiation each patient will be exposed to in this study is

approximately 12 mSv.
If patient participates in scientific research involving exposure to radiation more often, the patient should discuss with the investigator whether participation at this moment would be safe.
The radiation used during the study may lead to damage to patient's health. However, this risk is small. We nevertheless advise you not to participate in another scientific study involving exposure to radiation in the near future. Examinations or procedures involving radiation for medical reasons are not a problem.

MRI Scan
MRI scanners use a large magnet and radio waves to take pictures of the body. The scanning takes about 30 to 60 minutes depending on what part of body is scanned. The effects of the magnetic fields in an MRI scanner have been widely studied. There are no known risks from being exposed to the magnetic fields. Before an MRI scan, patient will be asked a series of questions by the MRI staff to be sure that they do not have any medical reasons that stop you from having an MRI. Patient should not have an MRI if you have a pacemaker, metallic cardiac valve(s), or certain types of metallic aneurysm clips. Patient should not have an MRI if have implanted electronic infusion pumps or other metallic pieces in their body. For some MRI scans, patients may get an MRI contrast material. This contrast material is given in patient's vein. Patient will not get the MRI contrast material if patient have abnormal kidney function. It is uncommon, but patient may feel warmth or pain in the area where the needle was inserted. Patient may also have nausea, vomiting, or headache. Serious allergic reactions that may be life threatening are very rare.

Electrocardiogram (ECG)
An ECG is used to check any problems with the electrical activity of the heart. Skin irritation from the ECG electrode pads or pain when removing the pads are possible side effects.

Electroencephalogram (EEG)
An EEG is used to check any problems with electrical activity of the brain. Skin irritation from the ECG electrode pads or pain when removing the pads are possible side effects. It also takes a long time to connect someone to an EEG machine, as dozens of electrodes have to be attached to patient's head and various gels, salt solutions, and/or pastes will be used to keep the electrodes in place.

Unknown Risks
There may be risks that are currently not known or cannot be predicted. Subject's condition may worsen, remain the same, or improve as a result of taking part in this research study.
Some side effects may not be known yet.

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

1.Men and women aged *55 years.
2.Subject or subject*s legally authorized representative is willing and able to provide written informed consent.
3.Probable DLB and identified cognitive deficits, according to current consensus criteria (McKeith et al, 2017), specifically one core clinical feature and a positive DaTscan. If a negative DaTscan, but the subject has historical PSG-verified RBD, the subject would also qualify.
4. MMSE score of 15-28, inclusive, during Screening.
5.Currently receiving cholinesterase inhibitor therapy, having received such therapy for greater than 3 months and on a stable dose for at least 6 weeks at the time of randomization. Except for reducing the dose for tolerability reasons, the dose of cholinesterase inhibitor may not be modified during the

study.
6.Normal or corrected eye sight and auditory abilities, sufficient to perform all aspects of the cognitive and functional assessments.
7.No history of learning difficulties that may interfere with their ability to complete the cognitive tests.
8.Must have reliable informant or caregiver.

Exclusion criteria

1. Diagnosis of any other ongoing central nervous system (CNS) condition other than DLB, including, but not limited to, post-stroke dementia, vascular dementia, Alzheimer*s disease (AD), or Parkinson*s disease (PD).
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 C-SSRS, or history of suicide attempt in previous 2 years, or, in the Investigator*s opinion, at serious risk of suicide.
3. Ongoing major and active psychiatric disorder 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. 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 interfere with assessment of drug safety.
6. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio (INR) >1.5.
7. Known human immunodeficiency virus, hepatitis B, or active hepatitis C virus infection.
8. Participated in a study of an investigational drug less than 3 months or 5 half-lives of an investigational drug, whichever is longer, before enrollment in this study.
9. History of previous neurosurgery to the brain.
10. If male with female partner(s) of child-bearing potential, unwilling or unable to adhere to contraception requirements specified in the protocol.
11. If female who has not has not reached menopause >1 year previously or has not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy, has a positive pregnancy test result during Screening and/or is unwilling or unable to adhere to the contraception requirements specified in the protocol.

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):	30-09-2019
Enrollment:	13
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	22-07-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-04-2020
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	EUCTR2019-001566-15-NL
CCMO	NL70403.056.19