A double-blind, placebo-controlled, five-way partial crossover study with EVP-6124 and donepezil in the scopolamine challenge model in healthy elderly volunteers

Published: 23-12-2011
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Primary Objectives:• Assess the pharmacokinetic (PK) and pharmacodynamic (PD)/efficacy effects of 3 different single doses of EVP-6124 vs. placebo;• Assess the PK and PD/efficacy effects of the different combinations of 2 doses of donepezil and 3...

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

Summary

ID

NL-OMON37445

Source
ToetsingOnline

Brief title
EVP-6124-donepezil interaction study in scopolamine model

Condition

- Mental impairment disorders

Synonym
Alzheimer's Disease, dementia

Research involving
Human

Sponsors and support

Primary sponsor: EnVivo Pharmaceuticals
Source(s) of monetary or material Support: EnVivo Pharmaceuticals

Intervention

Keyword: a7 nicotinic receptor agonist, donepezil, healthy volunteers, scopolamine model

Outcome measures

Primary outcome

Pharmacodynamics:

* Saccadic eye movements

* Smooth pursuit eye movements

* Adaptive tracking

* Visual analogue scales (VAS) for alertness, mood, calmness and psychedelic

effects

* Body sway

* Finger tapping

* Pharmaco-Electroencephalography EEG (pEEG)

* Visual verbal memory test (VVLT)

* Stroop color-word interference

* Pupil size

* N-back test

* Symbol digit substitution test

* Simple reaction time

Pharmacokinetics:

* Plasma PK EVP-6124: Cmax, Tmax

* Plasma PK donepezil: Cmax, Tmax

* Plasma PK scopolamine: Cmax, AUC0-last, AUC0-*, Tmax, t1/2β

Determination of genes related to acetylcoline receptor and

acetylcholinesterase transcription

Secondary outcome

- the difference in respons of tumor necrosis factor α (TNFα) to a

lipopolisacharide (LPS) challenge between treatment regimens will be assessed.

- Safety parameters: Adverse events (AEs), vital signs including blood pressure

measurements and weight, physical examinations including a neurological

assessment, 12-lead electrocardiograms (ECGs), and clinical laboratory tests

Study description

Background summary

EVP-6124 is a direct agonist of the α7 nicotinic acetylcholine receptor (α7nAChR), which is located in several brain areas involved in memory and cognition. Animal experiments showed improvement of scopolamine induced amnesia at doses of 0.3 and 1.0 mg/kg EVP-6124. It was also shown in this model that when EVP-6124 is co-administered with donepezil, an acetylcholinesterase inhibitor (AChEI), lower doses of both lead to similar reversal of scopolamine induced cognitive deficits than when either compound is given alone at that same dose. It is hypothesized that a nicotinic acetylcholine receptor agonist potentiates the effect of acetylcholine (ACh), by occupation of one of the two acetylcholine binding sites on the α7 nicotinic receptor. In a multiple ascending dose study in healthy volunteers, improvements of cognitive function were shown at doses up to 4.0 mg, particularly in learning, memory and in visual motor function. At a higher dose (10 mg), there was some evidence for a slowing of psychomotor and visual attention function, which might be

preliminary evidence of desensitization that occurs at higher dose levels.

The most widely prescribed drug treatments for the symptomatic treatment of mild-to-moderate Alzheimer*s disease (AD) are the AChEIs. These compounds improve memory and attention by increasing the ACh level in the brain. Since peripheral ACh levels are also elevated, treatment with AChEIs may lead to systemic side effects, such as nausea and vomiting. When lower doses of a AChEI can be given due to potentiation of the ACh effect by co-treatment with EVP-6124, this may reduce peripheral cholinergic side effects and hence increase the therapeutic window of AChEIs. Co-treatment may also lead to a more effective improvement of cognitive functions by potentiation of central α7 nicotinic effects.

Study objective

Primary Objectives:
• Assess the pharmacokinetic (PK) and pharmacodynamic (PD)/efficacy effects of 3 different single doses of EVP-6124 vs. placebo;
• Assess the PK and PD/efficacy effects of the different combinations of 2 doses of donepezil and 3 doses of EVP-6124;
• Determine which of these dose combinations of donepezil and EVP-6124 vs. placebo is the most effective in reducing scopolamine-induced cognitive deficits;

Secondary Objectives:
• Evaluate the safety of EVP-6124 vs. placebo;
• Evaluate the safety of EVP-6124 in combination with donepezil vs. placebo;
• Assess the exposure-response relationship for EVP-6124, donepezil and the combination of both;
• Assess the effect of EVP-6124 vs. placebo on inflammatory markers ex vivo.

Study design

This will be a double-blind, placebo-controlled, 5-way partial crossover design with three parallel cohorts of healthy elderly volunteers, each receiving a scopolamine challenge, a fixed dose of donepezil varying between cohorts, and3 different doses of EVP-6124 with a wash-out of two weeks between each study period

Intervention

a fixed dose of donepezil varying between cohorts, and3 different doses of EVP-6124

Study burden and risks

Across all studies adminitrating EVP-6124, donepezil, scopolamine or a combination of these drugs, adverse events were mild or sometimes moderate. Main adverse effects to be expected are nausea, vomiting and diarrhoea. These possible side effects are expected to be mild and transient.

Contacts

Public
EnVivo Pharmaceuticals

Arsenal Street 500
Watertown MA 02472
US
Scientific
EnVivo Pharmaceuticals

Arsenal Street 500
Watertown MA 02472
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Age between 65 and 85 years (inclusive) ;
2.Body mass index between 18 and 32 kg/m2;
3.Able to read and understand the written consent form, complete study-related procedures, and communicate with the study staff;
4.Non-smokers;

5.Willing to comply with study restrictions;

Exclusion criteria

1. Clinically relevant history of abnormal physical or mental health interfering with the study as determined by medical history taking and physical examinations obtained during the screening visit and/or at the start of the first study day for each period as judged by the investigator;;2. Clinically relevant abnormal laboratory results, electrocardiogram (ECG) and vital signs, or physical findings at screening and/or at the start of the first study day for each period (as judged by the investigator);;3. Mini-Mental State Examination (MMSE) lower than 27;;4. Positive test for hepatitis B, C or HIV;;5. History of alcoholism or substance abuse within three years prior to screening;;6. Subjects unable to refrain from alcohol use from 24hours prior to dosing on Day 1 Periods 1-5 until discharge from the CRU for each study period; ;7. Used tobacco and/or nicotine-containing products within 90 days of dosing on Day 1 Period 1;;8. Have a hemoglobin value of <8.0 mmol/L at screening;;9. Have aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT) or total bilirubin levels >1.5 times the upper limit of normal at screening;;10. Have evidence of significant renal insufficiency, indicated by a serum creatinine greater than the upper limit of normal at screening;;11. Evidence of elevated blood pressure at screening or baseline of >160 mmHg systolic or >100 mmHg diastolic;;12. Have a screening ECG with a corrected QT (QTc) interval using Bazett*s formula >450 msec for males and >470 msec for females or the presence of any clinically significant cardiac abnormalities, including but not limited to patterns consistent with myocardial ischemia, electrolyte abnormalities, or atrial or ventricular dysrhythmia or significant conduction abnormalities;;13. Subject is a habitual and heavy consumer of caffeinated beverages (more than 6 cups of coffee or equivalent/day) at screening and/or is not able to refrain from use of (methyl) xanthines (e.g. coffee, tea, cola, chocolate) from 12 hours prior to dosing on Day 1 until discharge from the CRU for each study period;;14. Positive urine drug screen (UDS) or alcohol or cotinine test at screening and/or Day -1 of each period;;15. Concomitant use of inhibitors of CYP2D6 (e.g., kinidine, paroxetine, fluoxetine) or of CYP3A4 (e.g., ketoconazol, ritonavir) within 21 days of randomization on Day 1 Period 1;;16. Subject is unable to refrain from the use of concomitant medication which, in the opinion of the investigator, interferes with their ability to participate in the trial, from 7 days prior to dosing on Day 1 Period 1 until the follow-up study visit;;17. Subject has a history of severe allergies, or has had an anaphylactic reaction to prescription or non-prescription drugs or food;;18. History or clinical evidence of any disease and/or existence of any surgical or medical condition which might interfere with the absorption, distribution, metabolism or excretion of the study drugs (EVP-6124, donepezil or scopolamine);;19. Participation in an investigational drug trial in the 3 months prior to administration of the initial dose of study drug (Day 1 Period 1) or more than 4 times per year;;20. Donation of blood/plasma outside limits of Sanquin Blood Supply Foundation guidelines of approximately 500 mL or significant blood loss;;21. Have participated as a plasma donor in a plasmapheresis program within 7 days before screening;;22. Have received treatment with other nicotinic receptor agonists within 3 months of screening or previously received EVP-6124;;23. Have a history of an allergic reaction to nicotine containing products;;24. Subject does not have veins suitable for canula placement on both arms;;25.

Any other condition that in the opinion of the investigator would complicate or compromise the study, or the well being of the subject.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-01-2012
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	aricept
Generic name:	donepezil hydrochloride
Product type:	Medicine
Brand name:	scopolamine
Generic name:	scopolamine hydrobromide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	23-12-2011

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-03-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-09-2012
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	EUCTR2011-006016-31-NL
CCMO	NL38837.056.11