A Double-Blind, Placebo-Controlled, 5-Way Crossover Study of EVP-6124 in a Scopolamine Challenge Model in Healthy Elderly Subjects

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Primary objectives:To determine the exposure-response relationship of EVP-6124 over a range of plasma concentrations in a scopolamine-induced cognitive deficit model in healthy elderly subjects.Secundary objectives:To determine the exposure-response...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON41062

Source
ToetsingOnline

Brief title
Neurologic effects of EVP-6124 in healthy elderly.

Condition

- Neurological disorders NEC
- Cognitive and attention disorders and disturbances

Synonym
N/A as the study is in healthy volunteers

Research involving
Human

Sponsors and support

Primary sponsor: FORUM Pharmaceuticals Inc.
Source(s) of monetary or material Support: FORUM Pharmaceuticals Inc.

Intervention

Keyword: desensitization, EVP-6124, scopolamine challenge

Outcome measures

Primary outcome

Pharmacodynamics: Adaptive Tracking Test, Finger Tapping Test, N-back test,

Milner maze test, Visual Verbal Learning Test, Saccadic Eye Movement testing,

Pupil / iris ratio measurement, EEG and auditory Event-Related Potential tests.

Inflammatory ex vivo challenge: different cytokines.

Pharmacokinetics: PK plasma samples of scopolamine, EVP-6124 and metabolites.

Safety and tolerability: adverse events, clinical chemistry, hematology, urine

tests, heart and respiratory rate, blood pressure, temperature, ECG, physical

examination, and various questionnaires.

Secondary outcome

Not applicable.

Study description

Background summary

EVP-6124 is a drug acting as a partial agonist of the α7 nicotinic acetylcholine receptor. This receptor is localized mainly in the bran in diverse areas known to principally influence cognition and memory. In preclinical research, administration of 0.3 and 1.0 mg/kg EVP-6124 showed a significant improvement of the cognitive deficit given by scopolamine, nevertheless higher concentrations resulted in a decrease of such improvement. Similar results were seen in a FIM study (EVP-6124-001) where in the subjects

with the highest dose arm of the study, a decrease in the cognitive improvement was verified. The current study is being conducted to better understand the exposure-response relationship of EVP 6124 to cognition, and to identify if desensitization might occur, and if so, at what dose/plasma concentrations. The doses selected for this study (10, 30, 60, and 80 mg EVP 6124 HCl compared to placebo) were chosen to better approximate the plasma concentration levels that would be achieved at steady state following daily dosing in the Alzheimer*s disease and schizophrenia patients studies (1, 2, and 3 mg/dag).

Study objective

Primary objectives:
To determine the exposure-response relationship of EVP-6124 over a range of plasma concentrations in a scopolamine-induced cognitive deficit model in healthy elderly subjects.

Secundary objectives:
To determine the exposure-response relationship of EVP-6124 over a range of plasma concentrations in healthy elderly subjects.
To evaluate the safety of EVP-6124 in healthy elderly subjects.
To explore the immunologic effects of EVP-6124 in an ex vivo inflammatory challenge model.

Study design

It is a double-blind, placebo-controlled, 5-period crossover study with EVP-6124 in a scopolamine challenge model in healthy elderly. In each study period, subjects will receive open-label, blinded scopolamine and EVP-6124 or placebo.

Intervention

Not applicable.

Study burden and risks

EVP-6124 has been administrated through various studies to more than 1000 patients and healthy subjects showing to be safe. The cognitive challenge model with scopolamine is frequently used with an acceptable side effects profile. Considering that the research will be performed in healthy elderly subjects, no health benefits could be expected.

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. ICF signed by the subject or legally acceptable representative before any study-specific procedures for the subject are performed.
2. Healthy males and females >=65 and <=80 years of age.
3. Body mass index of >=18 and <=35 kg/m2.
4. Subject has not smoked in 6 months and will continue to abstain throughout the study.
5. No history of relevant neurological or systemic illness that may interfere with study participation as assessed by the investigator.
6. MMSE score > 27.
7. Fertile, sexually active male subjects must use an effective method of contraception during the study. The female partner of male subjects must be surgically sterile (hysterectomy or bilateral tubal occlusion/ligation), postmenopausal for at least 1 year, or willing to practice adequate methods of contraception if of childbearing potential (defined as consistent use of

combined effective methods of contraception [including at least 1 barrier method]).
8. Able to read and understand the written consent form, complete study-related procedures, and communicate with the study staff.
9. Willing and able to comply with study restrictions (Section 8.3).

Exclusion criteria

1. History or presence of any clinically significant illness that, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results.
2. Presence (at Screening or Day -1 of Period 1) of abnormal laboratory or ECG results, vital signs, or physical findings that are considered clinically relevant by the investigator.
3. Positive test for hepatitis B, hepatitis C, or HIV.
4. History of alcoholism or substance abuse within 3 years prior to Screening.
5. Hemoglobin value of <8.0 mmol/L at Screening.
6. Aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT) or total bilirubin levels >1.5 times the upper limit of normal (ULN) at Screening.
7. Evidence of potential significant renal insufficiency, indicated by a serum creatinine value >178 µmol/L at Screening.
8. Evidence of elevated blood pressure >160 mmHg systolic or >100 mmHg diastolic at Screening or Baseline.
9. Presence at Screening of any clinically significant cardiac abnormalities including, but not limited to, patterns consistent with myocardial ischemia, electrolyte abnormalities, atrial or ventricular dysrhythmia or significant conduction abnormalities, or a corrected QT interval using Fridericia*s formula (QTcF) of >450 msec for males and >470 msec for females.
10. 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 (eg, coffee, tea, cola, chocolate) from 12 hours prior to dosing on Day 1 until discharge from the CRU for each study period.
11. Positive drug screen (including cotinine UDS and breath alcohol test) at Screening and/or Day -1 of Period 1.
12. History of severe allergies, an anaphylactic reaction to prescription or non-prescription drugs or food, or an allergic reaction to nicotine-containing products.
13. 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 or scopolamine).
14. Significant suicide risk as defined by: suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year, at screening or baseline; or, suicidal behaviors within 1 year before screening.
15. Participated in an investigational drug trial in the 3 months prior to administration of the initial dose of study drug (Day 1 Period 1).
16. Donation of blood/plasma outside limits of Sanquin Blood Supply Foundation guidelines of approximately 500 mL or significant blood loss within 3 months prior to Screening.
17. Donation of plasma in a plasmapheresis program within 7 days prior to Screening.
18. Received treatment with other nicotinic receptor agonists (eg, varenicline) within 3 months of Screening.

19. Veins unsuitable for cannula placement on both arms.
20. An employee of the Sponsor or CRU personnel directly affiliated with this study or their immediate family member defined as a spouse, parent, child or sibling, whether biological or legally adopted.

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):	03-11-2014
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	EVP-6124 HCl Monohydrate
Generic name:	EVP-6124

Ethics review

Approved WMO

Date:	17-09-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	27-10-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2014
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	EUCTR2014-003028-30-NL
CCMO	NL50350.056.14