# A randomized, double-blind, placebo-controlled, single dose, 3-way cross-over study in healthy elderly subjects to develop an anti-cholinergic pharmacological challenge with biperiden.

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• To determine the profile of CNS effects at several time points after 2 mg and 4 mg biperiden in comparison to placebo in healthy elderly subjects.• To investigate the safety and tolerability of biperiden in healthy elderly subjects.• To determine...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Neurological disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON46604

**Source**
ToetsingOnline

**Brief title**
Biperiden challenge study

### Condition

- Neurological disorders NEC

**Synonym**
Alzheimer's disease

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Centre for Human Drug Research
**Source(s) of monetary or material Support:** CHDR

## Intervention

**Keyword:** Biperiden, challenge model, cognition, pharmacodynamics

## Outcome measures

### Primary outcome

Tolerability / safety endpoints

• Treatment-emergent (serious) adverse events ((S)AEs).

• Concomitant medication

• Clinical laboratory tests

• Vital signs (blood pressure, heart rate)

• Electrocardiogram (ECG)

Pharmacokinetic endpoints

• Plasma

Pharmacodynamic endpoints

• Saccadic eye movements

• Smooth pursuit eye movements

• Pupillometry

• Body sway

• Adaptive tracking

• Visual Analog Scales (VAS) according to Bond and Lader

• VAS Nausea

• N-Back task

• Visual Verbal Learning test (VVLT)

• EEG: power spectra (resting eyes closed, eyes open condition)

• ERPs: MMN

**Secondary outcome**

NA

# Study description

**Background summary**

Deficits in the cholinergic system have been found in both neurodegenerative and neuropsychiatric disorders. Anti-cholinergic pharmacological challenges have been used to induce symptoms of cognitive impairment in healthy subjects, reminiscent of neurodegenerative disorders such as Alzheimer*s disease (AD) or of those observed in schizophrenia. If a challenge model induces temporary (reversible) cognitive defects by affecting the same neurobiological mechanisms that are involved in these neurodegenerative disorders, it can be used as a pharmacological tool to investigate the cognitive effects of new pro-cholinergic compounds that are under development.
Biperiden is a selective M1 antagonist. Administration of biperiden has been shown to lead to impairments in episodic and working memory (1-3), selective attention and post-error processing (4, 5). Because of the selectivity of biperiden, a biperiden challenge model would be more appropriate to demonstrate pharmacological effects of the new specific muscarinic agonists that are under development, than the scopolamine model. Several studies have been reported which have investigated biperiden as a cognitive challenge model in different groups including healthy young (4, 6), healthy elderly (1), and schizophrenia patients (7). Also in animals (primarily rodents) the cognitive diminishing effects of muscarinic blockage by biperiden have been identified (3). These studies have, however, significant design-related limitations: only one session of testing was performed post dose, in most cases around the Tmax of biperiden (approximately 1 hour post dose). It is not always described whether the test battery was also performed before drug administration, to serve as baseline measurement. Also, the relation between cognitive pharmacodynamic (PD) effects

and the plasma pharmacokinetics (PK) of biperiden was not investigated as in most cases the PK was not analysed.
In this study we aim to validate biperiden as a cognitive challenge model to be used for proof-of-pharmacology of selective muscarinic M1 agonists. We will investigate two dose levels of biperiden in healthy elderly subjects, and we will perform PD testing on mulitple time points using a comprehensive computerised central nervous system (CNS) test battery (NeuroCart) to explore the duration of the biperiden effect and to observe when the maximum PD effect is reached. By measuring biperiden plasma concentrations at multiple time points, we will be able to determine potential plasma concentration-effect relationships. The effects of biperiden will be compared with placebo using a double blind within-subject 3-way cross-over design.

**Study objective**

• To determine the profile of CNS effects at several time points after 2 mg and 4 mg biperiden in comparison to placebo in healthy elderly subjects.
• To investigate the safety and tolerability of biperiden in healthy elderly subjects.
• To determine the pharmacokinetics of biperiden in healthy elderly subjects

**Study design**

Single-centre, randomised, double-blind, placebo-controlled, 3-way cross-over study in healthy male and female elderly subjects.

**Intervention**

Biperiden 2mg and biperiden 4mg and placebo.

**Study burden and risks**

This study design has been used previously in many entry-into-man studies, and is accepted by scientists and regulatory authorities. All study drug administrations will be done in the clinic under medical supervision. The subjects receiving any study drug will remain in the clinic for at least 22 hours after each study drug administration. Thus, the subjects can be closely monitored for any adverse signs during the different treatments. Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study.

# 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. Elderly male or female subjects aged between 65 and 80 (inclusive) years old;
2. Healthy subjects as defined by the absence of evidence of any active or chronic disease following detailed medical and surgical history review and a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry, and urinalysis;
3. BMI between 18 and 34 kg/m2, inclusive;
4. Female subjects should be postmenopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level at screening (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women.
5. Able to understand the commitments of the study and to communicate effectively with the investigator and site staff;
6. Absence of cognitive impairment evident by a score of 28 or higher on the Mini Mental

State Examination (MMSE);
7. Able to participate and willing to give written informed consent and to comply with the study restrictions.

## Exclusion criteria

1. Clinically relevant history of abnormal physical or mental health interfering with the study as determined from the medical history review and the 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 (including (but not limited to), neurological, psychiatric, endocrine, cardiovascular (including recent myocardial infarction), respiratory, gastrointestinal, hepatic, renal disorder or presence of narrow-angle glaucoma).
2. 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.
3. Any disease associated with cognitive impairment, including but not limited to schizophrenia and dementia.
4. History of severe allergies, or history of an anaphylactic reaction to prescription or non-prescription drugs or food.
5. History of hypersensitivity to biperiden or to the excipients used in the biperiden formulation (Maize starch, Lactose monohydrate, Microcrystalline cellulose, Calcium hydrogen phosphate, Copovidone, Talc, Magnesium stearate, Potato starch)
6. Positive test for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
7. Positive urine drug screen (UDS), or alcohol test at screening and/or upon admission to the Clinical Research Unit (CRU).
8. 8. Presence or history (within 3 months of screening) of alcohol abuse confirmed by medical history, or daily alcohol consumption exceeding 2 standard drinks per day on average for females or exceeding 3 standard drinks per day on average for males (1 standard drink = 10 grams of alcohol), and the inability to refrain from alcohol during the visits until discharge from the CRU (alcohol consumption will be prohibited during study confinement).
9. Use of tobacco and/or nicotine-containing products within 90 days of dosing and throughout the study until follow-up.
10. 10. Excessive caffeine consumption, defined as >800 mg per day from 7 days prior to the first dose of the study drug until 24 hours prior to dosing. Subjects will abstain from caffeine-containing products for 24 hours prior each dosing and whilst in the study unit until discharge from the study unit. At other times throughout the study, subjects should not consume more than 800 mg caffeine per day. Caffeine quantities defined as: one cup of coffee contains 100 mg of caffeine; one cup of tea, or one glass of cola, or potion of chocolate (dark:100 g, milk 200 g) contains approximately 40 mg of caffeine; one bottle of Red Bull contains approximately 80 mg of caffeine.
11. Any other concurrent disease or condition that could interfere with, or for which the concomitant treatment might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.
12. Participation in an investigational drug trial in the 3 months prior to administration of the

initial dose of study drug or more than 4 times per year.
13. Donation or loss of blood of more than 500 mL within 3 months (males) or 4 months (females) prior to screening.
14. Use of concomitant medications within 14 days prior to study drug administration or within 5 half-live (whichever is longer). For details see section 4.4.

# Study design

## Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Crossover |
| Masking: | Double blinded (masking used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 19-09-2018 |
| Enrollment: | 12 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Akineton |
| Generic name: | biperiden |
| Registration: | Yes - NL outside intended use |

# Ethics review

Approved WMO

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| Date: | 14-02-2018 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |

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|---|---|
| | metc-ldd@lumc.nl |
| Approved WMO Date: | 13-06-2018 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

# 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 | EUCTR2017-004672-65-NL |
| CCMO | NL64171.058.17 |