A randomized, double-blind, placebo and reference controlled, multiple ascending dose study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of Memogain administered by intranasal application to healthy elderly subjects.

Published: 26-01-2016
Last updated: 20-04-2024

Objective(s)• To evaluate the safety and tolerability after intranasal administration of ascending multiple doses of Memogain in healthy elderly subjects.• To evaluate the PK after intranasal administration of ascending multiple doses of Memogain in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Dementia and amnestic conditions
Study type	Interventional

Summary

ID

NL-OMON43526

Source
ToetsingOnline

Brief title
Multiple ascending dose study with Memogain.

Condition

- Dementia and amnestic conditions

Synonym
Dementia and Alzheimer's Disease

Research involving
Human

Sponsors and support

Primary sponsor: NEURODYN LIFE SCIENCES INC
Source(s) of monetary or material Support: Neurodyn Inc.

Intervention

Keyword: Alzheimer, Memogain, pharmacodynamics, pharmacokinetics

Outcome measures

Primary outcome

Tolerability / safety endpoints

• Treatment-emergent (serious) adverse events ((S)AEs) up to 5 pharmacokinetic half-lives after study drug (i.e. Memogain) discontinuation.

• Treatment-emergent abnormalities in vital signs (blood pressure and pulse rate) until end of study (EOS).

• Treatment-emergent marked ECG abnormalities up to 5 pharmacokinetic half-lives after study drug discontinuation (i.e. Memogain).

• Treatment-emergent marked laboratory abnormalities up to 5 pharmacokinetic half-lives after study drug discontinuation (i.e. Memogain).

• The above 4 endpoints will also be investigated after galantamine administration in cohort 2

• Post-dose nasal examinations.

Pharmacokinetic endpoints

PK model

A population PK model will be developed to describe the pharmacokinetic profile of Memogain and galantamine in plasma. The estimated population values of the model parameters (both fixed and random effects) are used to determine individual empirical Bayes' estimates of the primary pharmacokinetic parameters such as CL/F, V/F and Vss/F, and of derived observable parameters including, but not limited to, Cmax, tmax, AUC-0-, and apparent terminal half-life. Additional PK parameters may be calculated if appropriate.

CSF

To investigate possible differences between concentration of galantamine cleaved from Memogain and concentrations of galantamine following oral administration in the central nervous system, CSF galantamine and Memogain concentrations will be compared within-subject in cohort 2 (Memogain 11mg). 12 subjects that were on active treatment in cohort 2 will be randomized to one of four different CSF sampling time points (i.e. 3 subjects per time point). In total, two CSF samples will be taken per subject (one after Memogain administration on Day 1, and one after galantamine oral administration) to characterise the time-concentration curve for Memogain and galantamine.

PK/PD relationship

The relationship between plasma Memogain and galantamine concentrations and a corresponding selection of relevant pharmacodynamic measurements will be plotted to evaluate the relationship graphically. If the observed pharmacodynamic effects allow it, a suitable PK/PD model will be developed to

describe the exposure/concentration-effect relationship.

Pharmacodynamic endpoints

NeuroCart tests, including:

• Adaptive tracking test

• EEG: 21-lead EEG recordings; standard power spectrum analysis

• Event related potentials (ERPs), i.e. P300

• Saccadic and smooth pursuit eye movements

• N-back task (0-back, 1-back and 2-back condition)

• Visual Verbal Learning test

• VAS according to Bond and Lader (alertness, mood, calmness) and nausea

Secondary outcome

n/a

Study description

Background summary

Alzheimer's Disease (AD) is the most common cause of dementia in the western world. Cholinergic dysfunction plays a major role in this disease. Galantamine is a nicotinic acetylcholine receptor modulator and cholinesterase inhibitor (CEI) and is used to treat patients with AD. However, patients treated with CEIs often experience side effects such as nausea and vomiting. Memogain® is a prodrug of galantamine that can be administered intranasally. It is thought to have a higher CNS penetration, thereby increasing its effectiveness with fewer peripheral side effects.
In this multiple ascending dose study, the safety, tolerability and pharmacokinetics (PK) of multiple doses of Memogain will be assessed. Additionally, the relationship between Memogain/galantamine concentrations (in blood and CSF) and pharmacodynamic effects (PD, e.g. Neurocart) will be modelled.

Study objective

Objective(s)
• To evaluate the safety and tolerability after intranasal administration of ascending multiple doses of Memogain in healthy elderly subjects.
• To evaluate the PK after intranasal administration of ascending multiple doses of Memogain in healthy elderly subjects.
• To evaluate the PD after intranasal administration of ascending multiple doses of Memogain in healthy elderly subjects.
• In cohort 2: To investigate possible differences in cerebrospinal fluid (CSF) galantamine concentrations following administration of oral galantamine and intranasal Memogain.

Exploratory Objective
• To evaluate the PK-PD relationship after intranasal administration of ascending multiple doses of Memogain in healthy elderly subjects.

Study design

This will be a randomized, double blind, placebo controlled, sequential cohort, multiple ascending dose study in 48 healthy elderly subjects. 12 subjects in cohort 2 will return for galantamine administration and CSF measurement. The time between the two Memogain doses is 9 hours.

Intervention

Memogain will be administered intranasally for 7 days b.i.d. (14 doses in total). The 12 subjects from cohort 2 that were on Memogain treatment will be administered galantamine 16 mg once, as well as have lumbar punctures.

Study burden and risks

Galantamine hydrobromide
Galantamine hydrobromide (referred to as galantamine throughout this ABR , brandname Reminyl® EU), is approved by the European Medicines Agency and the Dutch health authority for the treatment of dementia of the Alzheimer*s type. Serious skin reactions (Stevens-Johnson syndrome and acute generalized exanthematous pustulosis) have been reported in a very small minority of patients receiving galantamine hydrobromide. The doses used in this study do not exceed the level used in clinical practice. The risks are therefore considered to be minimal.

Memogain
Since Memogain is a pro-drug devoid of pharmacological activity, it is expected that the systemic effects of Memogain will be attributable to its cleavage product galantamine. The side effect profile is expected to be favourable to

galantamine, at similar brain galantamine brain concentrations. However, there is evidence from a number of studies that intranasal administration is associated with local irritation.
Results from the single ascending dose study with Memogain in 5 cohorts of 5,5; 11; 22; 33; and 44 mg respectively, led to the following conclusions: All treatment-emergent adverse events (TEAEs) were mild or moderate of intensity and were self-limiting. There were no serious adverse events (SAEs). Memogain was well tolerated and did not result in clinically significant changes in blood and urinary laboratory values, vital signs and ECG safety parameters and there were no clinically significant changes in these values compared with values at baseline.

The incidence of nausea after administration of the highest Memogain dose levels (i.e. 33 and 44 mg) was reported in 50% (3 out of 6) subjects. In the present study the highest dose administered b.i.d. will be 22 mg. Compared to the oral administration of galantamine, administration of Memogain resulted in a larger proportion of TEAEs that were related to the respiratory, thoracic and mediastinal Symptom Organ Classes (SOCs). These TEAEs were observed in all Memogain dose levels, were relatively comparable for Memogain 5.5, 11, 22 and 33 mg and comprised mainly nasal discomfort and rhinorrhoea. Headache and somnolence were most often reported by subjects administered placebo. The nasal examinations showed abnormalities in the form of dry white plaques in the nose and to a lesser extent red and irritated nasal mucosa in the Memogain 44 mg cohort only.

Memogain may have drug related side effects such as dizziness and nausea. Subjects will remain in the clinic under supervision following the first 3 intranasal administrations, thus the subjects can be closely monitored for any adverse signs during the different treatments. Subjects will be discharged by a physician or nurse practicioner only if their medical condition allows. Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study.

Contacts

Public
NEURODYN LIFE SCIENCES INC

University Ave 550
Charlottetown PE C1A 4P3
CA
Scientific
NEURODYN LIFE SCIENCES INC

University Ave 550
Charlottetown PE C1A 4P3
CA

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Healthy male or postmenopausal female subjects, aged 65 years and over. Healthy status is defined by the absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead electrocardiogram (ECG), haematology, blood chemistry, and urinalysis;
2. Body Mass Index (BMI) between 18 kg/m² and 30 kg/m², inclusive, and with a minimum weight of 50 kg;
3. Able to participate and willing to give written informed consent and to comply with the study restrictions;
4. Absence of cognitive impairment evident by a score of 26 or higher on the Mini Mental State Examination (MMSE);
5. Non-smokers.

Exclusion criteria

1. Legal incapacity or inability to understand or comply with the requirements of the study;
2. 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;
3. Any disease associated with cognitive impairment, including (but not restricted to) schizophrenia and dementia;
4. Clinically relevant abnormal laboratory results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), 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). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects;
5. Systolic blood pressure (SBP) greater than 145 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg;
6. Notable resting bradycardia (HR < 45 bpm) or tachycardia (HR > 100 bpm) at screening or baseline visit;
7. Male: QtcF >450 or <300 msec at screening or baseline visit;; Female QtcF >460 or <300 msec at screening or baseline visit
8. Positive test for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening;
9. 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), or a positive breath alcohol test at screening or upon admission to the Clinical Research Unit (CRU), and the inability to refrain from alcohol use from 24 hours before screening, dosing and each scheduled visit until discharge from the clinical research unit (CRU) (alcohol consumption will be prohibited during study confinement);
10. Subject is unable to refrain from alcohol use from 24 hours prior to dosing until discharge from the CRU;
11. Used tobacco and/or nicotine-containing products within 90 days of dosing;
12. Positive urine drug screen (UDS) or alcohol or cotinine test at screening and/or pre-dose;
13. Habitual and heavy consumption of caffeinated beverages (more than 8 cups of coffee or equivalent/day) at screening and/or unable to refrain from use of (methyl) xanthine (e.g. coffee, tea, cola, chocolate) from 24 hours prior to dosing until discharge from the CRU
14. Aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT) or total bilirubin levels >1.5 times the upper limit of normal at screening;
15. Evidence of significant renal insufficiency, indicated by a glomerular filtration rate lower than the lower limit of normal (related to age) at screening;
16. Concomitant use of cholinergic (e.g. varenicline, donepezil, rivastigmine) or anti-cholinergic (e.g. clozapine, olanzapine) medication within 21 days prior to dosing;
17. Concomitant use of inhibitors or inducers of CYP2D6 (e.g., kinidine, paroxetine, fluoxetine) or of CYP3A4 (e.g., ketoconazol, ritonavir) within 21 days prior to dosing;
18. 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 21 days prior to dosing until the follow-up study visit;
19. Subject has a history of severe allergies, or has had an anaphylactic reaction to prescription or non-prescription drugs or food;
20. Known hypersensitivity to the investigational drug or comparative drug or drugs of the same class, or any of their excipients;
21. 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;
22. Result from nasal examination at screening that, in the investigator or physician*s opinion, could affect drug uptake following intranasal administration;
23. 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;
24. Donation or loss of blood of more than 500 mL within 3 months (males) or 4 months (females) prior to screening;
25. Any other condition that in the opinion of the investigator would complicate or compromise the study, or the wellbeing of the subject;
26. Unwillingness or inability to comply with the study protocol for any other reason

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):	07-03-2016
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Memogain
Generic name:	N/A
Product type:	Medicine
Brand name:	Reminyl
Generic name:	Galantamine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-01-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-02-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-03-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-04-2016
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	EUCTR2015-005533-42-NL
CCMO	NL56079.056.16