A randomized, double-blind, placebo-controlled multiple ascending dose study to assess safety, pharmacokinetics and pharmacodynamics of oral HTL18318 in healthy young adult and elderly subjects.

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1. To evaluate the safety and tolerability of ascending multiple oral doses of HTL18318 in healthy adult male and female subjects.2. To evaluate the pharmacokinetics of ascending multiple oral doses of HTL18318 in healthy adult male and female...

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

Summary

ID

NL-OMON46086

Source
ToetsingOnline

Brief title
Multiple ascending dose study of HTL18318

Condition

- Other condition
- Dementia and amnestic conditions

Synonym
Alzheimer's disease, dementia & schizophrenia

Health condition

Schizofrenie, Neurodegenerative disorders

Research involving
Human

Sponsors and support

Primary sponsor: Heptares Therapeutics Ltd.
Source(s) of monetary or material Support: Heptares Therapeutics Ltd.

Intervention

Keyword: HTL18318, pharmacodynamics, pharmacokinetics, safety

Outcome measures

Primary outcome

-Treatment-emergent (serious) adverse events ((S)AEs) until the end of

study (EOS) visit.

-Treatment-emergent abnormalities in vital signs (e.g. blood pressure

and pulse rate) until the end of study (EOS) visit.

-Treatment-emergent marked ECG abnormalities until the end of study

(EOS) visit.

-Treatment-emergent marked laboratory abnormalities until the end of

study (EOS) visit.

-Concomitant medication

-Salivary measurement

-Respiratory function measurement

-NeuroCart assessments:

*Adaptive Tracking test

*Milner Maze test (immediate, delayed and reversed condition)

*N-back test (0-back, 1-back and 2-back condition)

*Pupillometry

*Electroencephalography (EEG): 21-lead EEG recordings; standard

power spectrum analysis (optional: EEG analysis by NBT analytics)

*Event related potentials (ERPs) (i.e., P300 and mismatch-negativity

(MMN) tasks)

*Visual Analogue Scales according to Bond and Lader (alertness, mood,

calmness) and for nausea.

- Leeds sleep evaluation questionnaire

Secondary outcome

n.a.

Study description

Background summary

Increased life expectancy due to improved healthcare has raised the incidence and prevalence of neurodegenerative diseases, such as dementia, in the last decades. The most common cause of dementia is Alzheimer*s disease (AD) [1]. Research has shown that there is a significant and progressive loss of cholinergic neurons along with their cortically projecting axons in AD [3]. This cholinergic degeneration has been correlated to the cognitive decline seen in AD, and is supported by the temporary cognitive impairment in cognitively normal subjects induced by administration of the anticholinergic drug scopolamine [4] and the subsequent reversal by administration of physostigmine [5], a cholinesterase inhibitor (AChEI).
To date, no curative treatment is available for AD and patients can only benefit from drugs targeting symptomatic relief. The primary choice for symptomatic treatment are AChEIs, such as galantamine, donepezil and rivastigmine, which delay the breakdown of acetylcholine released into synaptic clefts, increasing the availability of acethylcholine (ACh) and thereby enhance cholinergic neurotransmission [6]. However, treatment with AChEIs often leads to gastrointestinal side effects (e.g. nausea, vomiting and diarrhea) associated with increased activation of peripherally located ACh receptors, causing dose limitations and a significant burden for patients.
There are two types of ACh receptors, namely nicotinic and muscarinic receptors (nAChRs and mAChRs). The mAChR family consists of 5 subtypes (M1-M5). M1 is the predominant mAChR in the central nervous system (CNS) and is found to be

expressed in the prefrontal cortex, striatum and hippocampus, brain areas associated with cognitive processes [7;8]. Drugs that target M1 receptors in particular may have cognitive enhancing potential while minimizing the negative side-effects seen in non-specific pro-cholinergic drugs, and could therefore provide potential benefit in the treatment of AD [9]. Selective M1 agonists may be expected to have the potential to produce a larger degree of cognitive enhancement than cholinesterase inhibitors because their dosing will not be limited by peripheral non-M1 mediated muscarinic adverse events and because their benefits do not depend on the existence of cholinergic tone within the CNS, unlike cholinesterase inhibitors.
HTL18318 is a M1 selective receptor agonist and a single ascending dose study including healthy young adult, healthy elderly and food interaction cohorts is currently being performed.

Study objective

1. To evaluate the safety and tolerability of ascending multiple oral doses of HTL18318 in healthy adult male and female subjects.
2. To evaluate the pharmacokinetics of ascending multiple oral doses of HTL18318 in healthy adult male and female subjects.
3. To evaluate the pharmacodynamics of ascending multiple oral doses of HTL18318 in healthy elderly male and female subjects.
4. To evaluate the safety and tolerability of ascending multiple oral doses of HTL18318 in healthy elderly male and female subjects.
5. To evaluate the pharmacokinetics of ascending multiple oral doses of HTL18318 in healthy elderly male and female subjects.
6. To evaluate the pharmacodynamics of ascending multiple oral doses of HTL18318 in healthy male and female subjects.

Study design

Single-centre, randomized, double-blind, placebo-controlled, multiple ascending dose study in healthy young adult and elderly subjects.

Intervention

In this study HTL0018318 will be administered in a oral solution.

Study burden and risks

The burden for the participants includes the time investment for the briefing, screening, the occasions and the follow-up visit. The occasions will consist of 20 days and 21 nights. Furthermore, subjects are asked to adhere to various lifestyle regulations. Blood and urine will be collected during the screening, occasions and the follow-up visit. Participants will be administered 20 oral

doses (1 per day) of HTL0018318 either as a fluid drink.

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. Young adults: age 18-55 inclusive. Elderly adults: age *65 years, inclusive.
2. Healthy young and elderly male and female subjects. Healthy status is defined by 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 ECG, haematology, blood chemistry, and urinalysis;
3. BMI between 18 and 34 kg/m2, inclusive;
4. Ability to communicate well with the investigator in the Dutch language;
5. Young female subjects (18-55 years inclusive) must have a negative serum pregnancy test at screening and urine pregnancy test pre-dose on Day 1. Women of childbearing potential

must consistently and correctly use (from screening, during the entire study, and for at least 90 days after last study drug intake) double barrier contraception (a condom combined with a method of contraception with a failure rate of < 1% per year), be sexually inactive, or have a vasectomized partner. Women not of childbearing potential are defined as postmenopausal (i.e., amenorrhea for at least 1 year without an alternative medical cause), or surgically or naturally sterile. Male subjects must consistently and correctly use (from screening, during the entire study, and for at least 90 days after last study drug intake) double barrier contraception (a condom combined with spermicide), be sexually inactive, or have a sterilized partner.
6. Able to participate and willing to give written informed consent and to comply with the study restrictions;
7. Willing and able to perform the cognitive tests, as evidenced by performance on the training session of the cognitive tests;

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 (including (but not limited to), neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder);
3. Any disease associated with cognitive impairment, including but not limited 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 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 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg or a history of a significant period of hypertension as judged by the principal investigator;
6. Notable resting bradycardia (HR < 45 bpm) or tachycardia (HR > 100 bpm) at screening or baseline visit;
7. A QTcF > 450 or < 300 msec at resting ECG at screening or baseline visit;
8. Personal or family history of congenital long QT syndrome or sudden death
9. Positive test for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening;
10. Aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT) or total bilirubin levels >1.5 times the upper limit of normal at screening;
11. Evidence of significant renal insufficiency, indicated by a glomerular filtration rate lower than the lower limit of normal (related to age) at screening;
12. 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)
13. Use of tobacco and/or nicotine-containing products within 90 days of dosing;
14. 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;
15. Positive urine drug screen (UDS), serum/urine pregnancy test for females of child-bearing potential or alcohol or cotinine test at screening and/or pre-dose;
16. Concomitant use of drugs that are inhibitors/inducers of CYP3A4 (e.g., ketoconazole, ritonavir) from 21 days prior to study drug administration;
17. Concomitant medication with a narrow therapeutic index that are substrates of CYP2C9 (e.g. coumarin anticoagulants)
18. Intake of any food or any drinks containing cranberry, pomegranate, star fruit, grapefruit, pomelos, exotic citrus fruits or Seville oranges (including marmalade and juices made from these fruits) within 3 days before admission to the CRU and while subjects are confined to the CRU;
19. 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 until the final follow-up study visit;
20. History of severe allergies, or history of an anaphylactic reaction to prescription or non-prescription drugs or food (non-active hay-fever is acceptable);
21. History of epilepsy or seizures of any kind at any time;
22. 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;
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 concomitant disease or condition that could interfere with, or for which the treatment of 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.

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):	01-03-2016
Enrollment:	99
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	HTL0018318
Generic name:	N.V.T.

Ethics review

Approved WMO Date:	23-02-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-07-2016

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-01-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2017
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	EUCTR2015-005807-10-NL
CCMO	NL56353.056.16