# A randomised, double blind, parallel, placebo controlled, drug-drug interaction study to investigate the safety, tolerability and pharmacokinetics of multiple doses of HTL0018318 given alone and in combination with donepezil at steady state in elderly volunteers.

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* To evaluate the safety and tolerability of adding multiple oral doses of HTL0018318 in elderly volunteers taking donepezil at steady state.* To compare the pharmacokinetic profiles of HTL0018318 and donepezil when given alone and in combination at...

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

## Summary

### ID

NL-OMON43229

**Source**
ToetsingOnline

**Brief title**
HTL0018318 and donepezil interaction study in elderly subjects.

### Condition

- Other condition
- Dementia and amnestic conditions

**Synonym**

Alzheimer's disease, dementia & schizophrenia

**Health condition**

Schizophrenia

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** donepezil, HTL0018318

## Outcome measures

**Primary outcome**

Tolerability/safety endpoints

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

- Concomitant medication

- Clinical laboratory tests

o Haematology

o Chemistry

o Urinalysis

- Vital signs

o Pulse Rate (bpm)

o Systolic blood pressure (mmHg)

o Diastolic blood pressure (mmHg)

- Electrocardiogram (ECG)

o Heart Rate (HR) (bpm), PR, QRS, QT, QTcF

- Holter 24 hours

Pharmacokinetic endpoints

Pharmacokinetics by non-compartmental analysis: Plasma and urine PK analysis of HTL0018318 Day 20 (and 45) to 27 (52); Cmax, Tmax, Ctrough, AUC (0-t, 0-tau, 0-infinity), *z, half-life, CLp/F and Vd/F, renal clearance and amount excreted in urine. Plasma PK analysis of donepezil (parameters as described for HTL0018318) at steady state (Day 19) and in combination with HTL0018318 (Day 20 to 24). Bank samples for genotyping will be collected for post hoc analysis if deemed necessary to interpret better the pharmacokinetic data. Metabolite profiling may be undertaken on selected or pooled samples, and reported separately.

**Secondary outcome**

Pharmacodynamic endpoints

- Visual Analog Scales (VAS) according to Bond and Lader to assess:

o mood (mm)

o alertness (mm)

o calmness (mm)

- VAS nausea (mm)

- Salivary measurement (g)

- Respiratory function

o Forced vital capacity (FVC)

o Volume forcedly expired in 1 second (FEV1)

o Peak Expiratory Flow (PEF) in litres per second

- Leeds Sleep Evaluation Questionnaire (LSEQ):

o Getting to sleep (GTS) (mm)

o Quality of sleep (QOS) (mm)

o Awake following sleep (AFS) (mm)

o Behaviour following wakening (BFW) (mm)

- Assessment of heart rate variability

# 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). Research has shown that there is a significant and progressive loss of cholinergic neurons along with their cortically projecting axons in AD. 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 and the subsequent reversal by administration of physostigmine, 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. 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. 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. 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.

## Study objective

* To evaluate the safety and tolerability of adding multiple oral doses of HTL0018318 in elderly volunteers taking donepezil at steady state.
* To compare the pharmacokinetic profiles of HTL0018318 and donepezil when given alone and in combination at steady state.
* To compare the peripheral pharmacodynamic effects of HTL0018318 and donepezil when given alone and in combination at steady state.

## Study design

All cohorts will be randomised, double-blind and placebo-controlled. Randomization is deemed appropriate to avoid selection bias for active compound or placebo treatment. A double-blind and placebo controlled design is deemed appropriate because of the pharmacodynamic measurements (e.g. Saliva flow, sleep quality, respiratory function) that will be performed in these parts of the study. By double-blinding the study, bias arising from study subject*s or investigator*s knowledge about treatment assignment is avoided. The dose level of HTL0018318 to be used will be chosen based on the pharmacokinetic and safety data obtained from the previous study HTL0018318-102/CHDR1527. Furthermore, the dose for cohort 3 in the current study will be decided based emerging data from cohort 1 and 2.

## Intervention

HTL0018318 will be administered in a oral solution in water.

## Study burden and risks

The burden for the participants includes the time investment for the briefing, screening, the occasions, return visits and the follow-up visit. The occasions will consist of 7 and 6 nights. There will be 6 return visits. Furthermore, subjects are asked to adhere to various lifestyle regulations. Blood and urine will be collected during the screening, occasions, return visits and the follow-up visit. Participants will be administered 5 oral doses of donepezil 5mg and 19 oral doses of donepezil 10mg, which could lead to gastrointestinal side effects.

Participants will also be administered 10 doses of HTL0018318 as a drink. HTL0018318 was generally well tolerated in study 18318-102, with no serious adverse events being reported. The adverse events that were most frequently

reported are headache, fatigue, somnolence, hot flushes, hyperhidrosis, chills and gastrointestinal symptoms. In all cohorts a change in blood pressure (increase) and heart rate (decrease) was measured. In the young and elderly subjects dosed with 20 mg, a small increase in the mean saliva production was observed. Overall, no clinically significant changes were seen on the ECGs and pulmonary function tests.

The conservative and careful selection of the starting dose is part of the safety strategy. HTL0018318 dose levels administered will not exceed the doses administered to healthy elderly subjects in the currently ongoing MAD study (CHDR1526/18318-102), i.e. 25 mg.

## 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. Able to understand the commitments of the study and to communicate effectively with the investigator and site staff;
5. If a woman of childbearing potential; must consent to and 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 vasectomised partner; otherwise women not of childbearing potential who are defined as postmenopausal (i.e., amenorrhea for at least 1 year without an alternative medical cause), or surgically or naturally sterile;
6. If a male subject; must consent to and 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 sterilised partner;
7. Able to participate and willing to give written informed consent and to comply with the study restrictions.

## 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 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, respiratory, gastrointestinal (including history of ulcer disease or gastrointestinal bleeding), hepatic, or renal disorder).
3. A recent (<5 years) history of any chronic respiratory problems such as asthma, recurrent chest infections, chronic obstructive pulmonary disease (COPD).
4. Any disease associated with cognitive impairment, including but not limited to schizophrenia and dementia.
5. A history of epilepsy or seizures of any kind at any time (except uncomplicated infantile febrile seizures).
6. History of severe allergies, or history of an anaphylactic reaction to prescription or non-prescription drugs or food (non-active hay-fever is acceptable).
7. History of hypersensitivity to donepezil, piperidine derivatives or to the excipients used in the donepezil formulation (lactose monohydrate, maize starch, microcrystalline cellulose, hyprolose, magnesium stearate, talc, macrogol, hypromellose, titanium dioxide and yellow iron oxide).

8. 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.
9. Systolic blood pressure (SBP) greater than 150 or less than 90 mm Hg, and/or diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg at screening and baseline or a history of a significant period of hypertension as judged by the principal investigator.
10. Notable resting bradycardia (HR < 45 bpm) or tachycardia (HR > 100 bpm) at screening or baseline visit.
11. A QTcF > 450 (for males) or >460 (for females) or < 300 msec at resting ECG at screening and baseline visit.
12. Personal or family history of congenital long QT syndrome, *sick sinus syndrome* or other supraventricular cardiac conduction conditions such as sinoatrial or atrioventricular block or sudden death.
13. Based on the results of the 24 hour period ECG Holter monitoring during screening, potential subjects can be excluded based on the following exclusion criteria: more than 200 ventricular ectopics in 24 hours. Ventricular tachycardia (defined as being three or more successive ventricular ectopic beats at a rate of at least 120 beats per min). Second degree heart block. Sustained cardiac arrhythmias (atrial fibrillation, SVT, complete heart block). Any symptomatic arrhythmia (except isolated extra systoles).
14. 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.
15. Positive test for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
16. Aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT) or total bilirubin levels >1.5 times the upper limit of normal at screening and baseline. Except if an elevated (mainly unconjugated) bilirubin of >1.5 fits the diagnosis Gilbert's syndrome judged by the research physician.
17. Evidence of significant renal insufficiency, indicated by a glomerular filtration rate lower than the lower limit of normal (related to age) at screening and baseline.
18. Positive urine drug screen (UDS), or alcohol test, or cotinine test, or serum pregnancy test for females of child-bearing potential at screening and/or pre-dose.
19. 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, 24 hours before and throughout each dosing period (donepezil and HTL0018318) and each scheduled visit until 2 days after discharge from the CRU (alcohol consumption will be prohibited during study confinement).
20. Use of tobacco and/or nicotine-containing products within 90 days of dosing and throughout the study until follow-up.
21. 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) during the stay in the CRU.
22. Intake of any food or 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 up to 3 days following final discharge from the CRU.
23. Concomitant use of drugs that are inhibitors/inducers of CYP3A4 and CYP2C9 (e.g. ketoconazole, rifampicin, fluconazole, carbamazepine) from 21 days prior to study drug administration.
24. Concomitant use of drugs that are inhibitors/inducers of CYP2D6 or that could interact with donepezil (e.g. quinidine, buproprion, paroxetine, fluoxetine, phenytoin, dextromethorphan, desimipramine, perphenazine, tolterodine or those with a narrow therapeutic index that are substrates of CYP2D6 (e.g. thioridazine, pimozide).
25. Concomitant medication with a narrow therapeutic index that are substrates of CYP2C9 (e.g. coumarin anticoagulants) or CYP3A4 (e.g. cyclosporine).
26. 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.
27. 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.
28. 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.
29. Donation or loss of blood of more than 500 mL within 3 months (males) or 4 months (females) prior to screening.

# Study design

## Design

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|---|---|
| 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): | 22-09-2016 |

| | |
|---|---|
| Enrollment: | 36 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | DONEPEZIL HYDROCHLORIDE |
| Generic name: | Donepezil |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | HTL0018318 |
| Generic name: | N/A |

## Ethics review

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|---|---|
| Approved WMO Date: | 16-09-2016 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 19-09-2016 |
| Application type: | First submission |
| 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 | EUCTR2016-003212-13-NL |
| CCMO | NL58837.056.16 |