HTL0018318 and donepezil interaction study in elderly volunteers.

Gepubliceerd: 28-10-2016 Laatst bijgewerkt: 18-08-2022

Not applicable

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON28309

Bron
NTR

Verkorte titel
Not applicable

Aandoening

Drug-Drug interaction, M1 agonist, Alzheimer, donepezil

Ondersteuning

Primaire sponsor: Heptares Therapeutics Ltd.
Overige ondersteuning: Sponsor (Heptares Therapeutics Ltd.)

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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.
PK

Toelichting onderzoek

Achtergrond van het onderzoek

Objectives:

• 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 and peripheral pharmacodynamic profiles of HTL0018318 and donepezil when given alone and in combination at steady state.

Doel van het onderzoek

Not applicable

Onderzoeksopzet

Not applicable

Onderzoeksproduct en/of interventie

HTL0018318 will be administered in a oral solution.

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Subjects must meet none of the following exclusion criteria at screening:

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 (Day 0) until collection of the final pharmacokinetic blood sample at Follow-up.

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.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	21-09-2016
Aantal proefpersonen:	36
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	28-10-2016
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL5915
NTR-old	NTR6195
Ander register	: CHDR1624

Resultaten

Samenvatting resultaten
Not applicable