Multiple ascending dose study of HTL0018318

Gepubliceerd: 22-03-2016 Laatst bijgewerkt: 18-08-2022

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

Samenvatting

ID

NL-OMON24000

Bron
NTR

Aandoening

Dementia, pharmacokinetics, pharmacodynamics

Ondersteuning

Primaire sponsor: Heptares Therapeutics Ltd.
Overige ondersteuning: Heptares Therapeutics Ltd.

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Safety and tolerability endpoints
- Treatment-emergent (serious) adverse events ((S)AEs)
- Concomitant medication
- Clinical laboratory tests (Haematology, Chemistry, Urinalysis)
- Vital signs (Pulse Rate (bpm), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg))
- Electrocardiogram (ECG) (Heart Rate (HR) (bpm), PR, QRS, QT, QTcF)
- pulmonary function test

- salivary flow rate.

Pharmacokinetics
- A population approach PK model will be developed, describing the plasma HTL0018318 concentrations over time.

Pharmacodynamics
- Adaptive Tracking
-Pupillometry-left pupil/iris ratio; right pupil/iris ratio
-Milner Maze test (immediate, delayed and reversed condition)
-N-back (0-back, 1-back and 2-back condition)
-Electroencephalography (EEG): 21-lead EEG recordings (standard power spectrum analysis; optional EEG analysis by NBT analytics)
-Event related potentials (ERPs) (i.e. P50, N100, P300 and mismatch-negativity (MMN) tasks)
-Visual Analogue Scales according to Bond and Lader (alertness, mood, calmness)
-Visual Analogue Scale for nausea.
-Leeds Sleep Evaluation Questionnaire"

Toelichting onderzoek

Achtergrond van het onderzoek

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 sideeffects
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.

Onderzoeksopzet

-Safety: day -1, pre dose. On day 1, 5 and 10:30m, 1h, 2h, 3h, 6h, 8h. Daily pre dose and 1.5 h post dose. 24 post last dose.

-PK: pre-dose, 15m, 30m, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h ,9h, 12h, 24h, and 30h, 48h, 72h post last dose.

-PD: pre-dose, 1h, 1.5h, 2.5h, 3h, 3.5h, 5h, 5.5h, 6h, 8h, 9h, on day 1, 5 and 10. Ohter days less frequent.

Onderzoeksproduct en/of interventie

In this study HTL0018318 will be administered in a oral solution

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Younger 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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

"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/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;

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 and 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 and baseline.

11. 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.
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 and CYP2C9 (e.g., ketoconazole, rifampicin, fluconazole, carbamazepine) 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) or CYP3A4 (e.g. cyclosporine);

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.

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:

26. More than 200 ventricular ectopics in 24 hours;

27. Ventricular tachycardia (ventricular tachycardia was defined as being three or more successive ventricular ectopic beats at a rate of at least 120 beats min-1);

28. Second degree heart block;

29. Sustained cardiac arrhythmias (atrial fibrillation, SVT, complete heart block);

30. Any symptomatic arrhythmia (except isolated extra systoles)."

Onderzoeksopzet

Opzet

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

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	21-03-2016
Aantal proefpersonen:	48
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	22-03-2016
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	NL5008
NTR-old	NTR5781
Ander register	: 18318-102

Resultaten