Single ascending dose study of HTL0018318

Gepubliceerd: 30-11-2015 Laatst bijgewerkt: 18-08-2022

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

Samenvatting

ID

NL-OMON26350

Bron
NTR

Aandoening

Dementia & schizophrenia
Pharmacokinetics
Pharmacodynamics
HTL0018318

Dementie & schizofrenie
Pharmacokinetiek
Pharmacodynamiek
HTL0018318

Ondersteuning

Primaire sponsor: Heptares Therapeutics Ltd.
Overige ondersteuning: Sponsor: 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) Pharmacokinetics A population approach PK model will be developed, describing the plasma HTL0009936 concentrations over time. Pharmacodynamics (Part 1 and 3 only) Adaptive Tracking test Visual Analogue Scale N-back test Milner MAZE test Pupil size EEG/ERP

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 [2]. 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 [3] and the subsequent reversal by administration of physostigmine [4], 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 acetylcholine (ACh) and thereby enhance cholinergic neurotransmission [5]. However, treatment with AChEIs often leads to gastrointestinal side effects (e.g. nausea, vomiting and diarrhoea) 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 [6;7]. 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 [8]. 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. Aside from the beneficial effect of drugs that target M1 receptors on AD, clinical research has demonstrated efficacy in schizophrenics [9]. Schizophrenia is a psychiatric disorder which afflicts approximately 1% of the population. Especially the cognitive impairments that are associated with this disease are not effectively treated with the current antipsychotic drugs. Research on M1 selective receptors in schizophrenia patients has shown a reduced receptor expression. This leads to the hypotheses that M1 selective receptor agonists might enhance

the receptor expression and reduce the cognitive deficits of schizophrenia patients [10].

Onderzoeksopzet

Part 1 and 3:

Safety: day -1, pre-dose, 30m, 1h, 2h, 3h, 6h, 8h, 24h, 30h, 48h, 72.

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

PD: pre-dose, 1h, 1.5h, 2.5h, 3h, 3.5h, 5h, 5.5h, 7h, 9h, 9.5h, 24h.

Part 2:

Safety: day -1, pre-dose, 30m, 1h, 2h, 3h, 6h, 8h, 24h, 30h, 48h, 72h.

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

CSF: subjects will be divided over time points: 2h, 6h, 8h.

Onderzoeksproduct en/of interventie

In this study HTL0018318 will be administered in a oral solution or a capsule if applicable.

Contactpersonen

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Healthy male 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;

2. BMI between 18 and 34 kg/m2, inclusive;

3. Ability to communicate well with the investigator in the Dutch language;

4. Able to participate and willing to give written informed consent and to comply with the study restrictions;

5. Willing and able to perform the cognitive tests, as evidenced by performance on the training session of the
cognitive tests;

Part 1 and 2 (healthy younger adult male subjects);

• Age 18 to 55 years, inclusive.

Part 3 (healthy elderly male and female subjects);

• Age ≥65 years, inclusive.

• Woman should be post-menopausal or naturally infertile.

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. A history of any chronic respiratory problems such as asthma, recurrent chest infections, COPD;

4. A history of epilepsy or seizures of any kind at any time;

5. Any disease associated with cognitive impairment, including but not limited to schizophrenia and dementia;

6. 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;

7. 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;

8. Notable resting bradycardia (HR < 45 bpm) or tachycardia (HR > 100 bpm) at screening or baseline visit;

9. A QTcF > 450 or < 300 msec at resting ECG at screening or baseline visit;

10. Personal or family history of congenital long QT syndrome or sudden death;

11. Positive test for Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human
immunodeficiency virus antibody (HIV Ab) at screening;

12. Aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT) or total
bilirubin levels >1.5 times the upper limit of normal at screening;

13. Evidence of significant renal insufficiency, indicated by a glomerular filtration rate lower than the lower limit of
normal (related to age) at screening;

14. 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);

15. Use of tobacco and/or nicotine-containing products within 90 days of dosing;

16. 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;

17. Positive urine drug screen (UDS) or alcohol or cotinine test at screening and/or pre-dose;

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. History of severe allergies, or history of an anaphylactic reaction to prescription or non-prescription drugs or
food (non-active hay-fever is acceptable);

20. 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;

21. 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;

22. Donation or loss of blood of more than 500 mL within 3 months (males) or 4 months (females) prior to
screening;

23. 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;

24. Part 1 and 2 (healthy younger adult subjects);

• No concomitant medication is allowed 21 days before start of the study till after the final visit;

25. Part 2

• Any contradictions for a lumbar puncture as judged by the principle investigator;

26. Part 3 (healthy elderly subjects);

• Concomitant use of drugs that are inhibitors/inducers of CYP3A4 (e.g., ketoconazole, macrolide antibiotics,
ritonavir, phenytoin) and CYP2C9 (eg fluconazole, amiodarone, carbamazepine, rifampicin) from 21 days prior to
study drug administration;

• Concomitant medication with a narrow therapeutic index that are substrates for CYP2C9 (eg coumarin
anticoagulants);

• 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.
Based on the results of the 24 hour ECG holter monitoring during screening, potential subjects for all parts of the
study can be excluded based on the following exclusion criteria:

• More than 200 ventricular ectopics in 24 hours.

• 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).

• Second degree heart block.

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

Onderzoeksopzet

Opzet

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

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	09-11-2015
Aantal proefpersonen:	72
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	30-11-2015
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	NL5521
NTR-old	NTR5648
Ander register	: 18318-101

Resultaten