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Safety and effectiveness of a novel drug for Alzheimer's disease on cognitive performance in the elderly

Submission date
01/05/2020

Registration date
07/05/2020

Last Edited
06/05/2020

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Nervous System Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
In the last decades, increased life expectancy due to improved healthcare has raised the incidence and prevalence of neurodegenerative diseases such as dementia. The most common cause of dementia is Alzheimer’s disease. Clinically, Alzheimer’s disease is characterized by a progressive decline of cognitive functions, particularly memory, leading to impairments of activities of daily living, work, and social life.

To date, no curative treatment is available for Alzheimer’s disease and patients can only benefit from drugs targeting the symptoms of the disease. The primary choice for treatment of Alzheimer's disease are cholinesterase inhibitors, which are often associated with gastrointestinal side effects (e.g. nausea, vomiting, and diarrhea).

HTL0009936 novel treatment that has been shown to have effectiveness in studies with rats and dogs. HTL0009936 has also been given to young and elderly volunteers at doses of 1-175mg, where it was generally well tolerated with no serious adverse events reported.

The aim of this study was to assess the effect of HTL0009936 on cognitive performance in elderly subjects with below-average cognitive function. HTL0009936 was administered both orally and as an infusion by the intravenous (IV) route. As this was the first time in which HTL0009936 was to be given IV, the assessment of the effect of HTL0009936 on cognition was preceded by an assessment of the safety and pharmacokinetics in normal healthy elderly patients when given IV in order to guide the design of an appropriate, well-tolerated dosing regimen.

Who can participate?
Healthy elderly (aged over 65 years) participants

What does the study involve?
The study consists of part A and B. In part A, subjects will be screened for participation, visit the Clinical Trial Unit 4 times at separate study days and will be screened at the end of the study. The duration of this Part A is a maximum of 20 weeks.

In Part B, subjects will be screened for participation and trained to be capable to perform all tests to assess cognitive functioning during the study. During 5 separate study days at the Clinical Research Unit, you will receive different treatments, intravenous and oral, and approximately one week after the administration of the treatment agent, you will be screened again. Totally, participation in Part B takes a maximum of 15 weeks.

What are the possible benefits and risks of participating?
The direct benefits or risks for those taking part in the study and how any adverse events will be managed.

Participation does not directly lead to any health-associated advantages for subjects, however, it does contribute to the current (lack of) knowledge in the field of Alzheimer research.

Screening and follow-up incorporates the close monitoring of adverse events that could be related or unrelated to the treatment under investigation. Subjects are under medical supervision of a study doctor of the Clinical Trial Unit.

Where is the study run from?
Centre for Human Drug Research (The Netherlands)

When is the study starting and how long is it expected to run for?
From December 2014 to May 2015

Who is funding the study?
Heptares Therapeutics Ltd. (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2014-004123-43

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
NL51371.056.14

Study information

Scientific Title
A two-part study to evaluate the safety, pharmacokinetics, pharmacodynamics of HTL0009936 in healthy elderly and elderly with below average cognitive functioning.

Acronym
HTL0009936

Study objectives
HTL0009936, as a potent and selective M1 receptor agonist, is hypothesized to enhance cognitive abilities in patients suffering from Alzheimer's disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/11/2014, Stichting Beoordeling Ethiek Biomedisch Onderzoek (BEBO) Ethics Committee (Postbus 1004, 9400 BA Assen, The Netherlands; info@stbebo.nl; +31 0592 405 871), ref: NL51371.056.14

Study design
Part A: An open-label sequential four-way cross-over study to assess safety, tolerability and pharmacokinetics
Part B: A five-way, randomized, placebo and comparator-controlled cross-over study of effectiveness

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)

Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Alzheimer's Disease

Interventions
Part A of the study assisted dose-finding for Part B of the trial. Start and end dates of Part B lead directly on from the end of Part A. The three dose levels of 13.5, 40 and 79.5 mg HTL0009936 and the infusion regimen in Part B were decided upon by the dose escalation committee in a dose decision meeting that preceded Part B of the study, based on a review of safety and PK data of Part A of the study.

The drug substance HTL0009936 was manufactured in accordance with Good Manufacturing Practice (GMP) at Shasun Pharma Solutions Ltd. (SPSL), Dudley, Cramlington, Northumberland, NE23 7QG, United Kingdom. HTL0009936 drug substance batch number 800261340 was used to generate the drug products for IV and oral administration.

Comparator products included physostigmine salicylate and glycopyrrolate bromide. Physostigmine salicylate was manufactured in accordance with GMP by the LUMC pharmacy, 2300 RC, Leiden, the Netherlands. Glycopyrrolate (glycopyrronium) bromide was manufactured in accordance with GMP by the Albert Schweitzer hospital, 3300 AK, Dordrecht, the Netherlands.

Placebo included 500 mL Sodium Chloride 0.9% bags were produced by Baxter Healthcare Ltd. Caxton Way, Thetford, Norfolk IP24 3SE, United Kingdom.

Treatment, randomisation, duration and follow-up
Part A:
Subjects were dosed between 9.20 and 12.30 in the morning following a standardized light breakfast. All subjects were dosed once per study period. Treatment arms were treated as follows:
1. HTL0009936 0.1 mg; intravenous for 30 minutes at 20 mL/h
2. HTL0009936 1 mg; intravenous for 30 minutes at 20 mL/h
3. HTL0009936 10 mg; intravenous for 30 minutes at 33.2 mL/h
4. HTL0009936 49.2 mg; intravenous; 14.1 mg HTL0009936 for 30 min at 47 mL/h and 35.1 mg HTL0009936 for 4.5 h at 13 mL/h
5. HTL0009936 83 mg; intravenous; 43 mg HTL0009936 for 2h at 64.8 mL/h and 40 mg HTL0009936 for 3h at 40.2 mL/h
6. HTL0009936 24 mg; oral dose
Treatment assignment was not applicable as all subjects that were enrolled in the study were treated according to the fixed order of treatments.

The total duration of the study for each subject was up to 88 days divided as follows:
1. Medical screening: up to 28 days (4 weeks) before occasion 1.
2. Study periods 1-3: admission on the evening of Day-1, study drug administration on Day 0,

discharge on the morning of Day 1. A minimum of two and a maximum of four weeks wash-out and analysis period.
3. Study period 4: admission on the evening of Day -1, study drug administration on Day 0, discharge on the morning of Day 1.
4. Follow-up visit: between 7 and 11 days after last study drug administration.

Part B:
Subjects were dosed between 10.30 and 13.30 in the morning/early afternoon following a standardized light breakfast. All subjects were dosed once per study period (5 study periods in total). Treatment arms were treated as follows:
1. HTL0009936 13.5 mg; intravenous; 4.5 mg for 1h at 83.3 mL/h and 9 mg for 4h at 41.7 mL/h
2. HTL0009936 40 mg; intravenous; 13.3 mg for 1h at 83.3 mL/h and 26.7 mg for 4h at 41.7 mL/h
3. HTL0009936 79.5 mg; intravenous; 26.5 mg for 1h at 83.3 mL/h and 53 mg for 4h at 41.7 mL/h
4. Physostigmine salicylate 0.83 mg; intravenous; 50 minutes at 50 mL/h (0.83 mg)
5. Placebo: saline solution intravenous; NaCl 0.9%; Regimen similar to active condition
Screening numbers were used before subjects were randomised to the treatment. Data collected at screening were recorded using the subject's initials, date of birth, and screening number as identifiers. Randomization was performed by the study statistician. Subject numbers were assigned to eligible subjects according to the pre-defined randomization list. Subjects were randomized in a consecutive order starting with the lowest number. Subjects were numbered 1001 through 1030. Replacement subjects were numbered +1000. The randomization code was generated using SAS version 9.1.3 by a study-independent statistician.

The total duration of the study for each subject was up to 67 days divided as follows:
1. Cognitive screening: up to 6 months before occasion 1.
2. Medical screening and CNS training: up to 28 days (4 weeks) before occasion 1.
3. Study periods 1-5: admission on the evening of Day-1, study drug administration on Day 0, discharge on the morning of Day 1. A minimum of one week and a maximum of two weeks wash-out period between drug administrations.
4. Follow-up visit occurred between 7 and 11 days after last study drug administration.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
HTL0009936 Physostigmine salicylate Glycopyrrolate bromide

Primary outcome measure
1. Safety assessed by monitoring and recording of adverse events (AEs), vital signs, ECG, 5-hour Holter monitoring, and safety chemistry and hematology blood sampling (9 to 15 times) within the first 8 hrs after starting the administration, at 12 and 24 hrs post-dose in parts A and B, and between 7 and 11 days post-dose in Part B.
2. Pharmacokinetics of HTL0009936 assessed through continuous urine collection. PK blood samples were collected according to the same schedule pre-dose (9 to 15 times) within the first 8 hrs after starting the administration, at 12 and 24 hrs post-dose in parts A and B, and between 7 and 11 days post-dose in Part B.

Secondary outcome measures

Pharmacodynamic oucomes in Part B
1. Vital signs assessed by systolic and diastolic blood pressure and pulse measurements taken after a minimum of 5 minutes rest in the supine position using an automatic oscillometric device at -28 days, pre-dose, 9 to 15 times within the first 8 h after starting the administration, at 12 and 24 h post-dose, and between 7 and 11 days post-dose.
2. Cognitive and neurophysiological functioning (NeuroCart and the Cambridge Neuropsychological Test Automated Battery (CANTAB) assessments at baseline (pre-dose) and between 1 h and 8 h post-treatment). Tests include:
2.1. Pupillometry at -28 days, pre-dose, and at 1, 3.5, 7.5 and 23.5 h after dosing
2.2. Milner Maze test at -28 days, pre-dose, and at 1, 3.5, 7.5 and 23.5 h after dosing
2.3. MMN at -28 days, pre-dose, and at 1.5, 4, and 8 h after dosing
2.4. VAS Nausea at -28 days, pre-dose, and at 1, 3.5, 7.5 and 23.5 h after dosing
2.5. N-back test at -28 days, pre-dose, and at 1, 3.5, 7.5 and 23.5 h after dosing
2.6. Adaptive tracking test at -28 days, pre-dose, and at 1, 3.5, 7.5 and 23.5 h after dosing
2.7. P300 at -28 days, pre-dose, and 1.5, 4, and 8 h after dosing
2.8. Pharmaco-electroencephalography (p-EEG) at -28 days, pre-dose, and at 1.5, 4, and 8 h after dosing
2.9. Leeds Sleep Questionnaire at pre-dose and 23.5 hrs after dosing
2.10. Paired Associates Learning (PAL) test assessed up to -28 days, pre-dose, and 5 and 24 h post-dosing
2.11. Rapid Visual Information Processing (RVIP) test assessed up to -28 days, pre-dose, and 5 and 24 h post-dosing
2.12. Spatial Working Memory (SWM) test assessed up to -28 days, pre-dose, and 5 and 24 h post-dosing
2.13. VVLT assessed up to -28 days and at 4 h after dosing

Overall study start date
29/09/2014

Completion date
01/07/2015

Eligibility

Key inclusion criteria
1. Aged 65+ years
2. Blood pressure ≤140/90 mmHg at screening
3. Heart rate between 45 and 100 bpm at screening

Participant type(s)
Healthy volunteer

Age group
Senior

Sex
Both

Target number of participants
Part A: 10 subjects. Part B: 33 subjects.

Key exclusion criteria
1. Use of antihypertensive drugs prior to and during the study period
2. Consumption of alcohol and caffeine-containing products, use of nicotine-containing products, and use of drugs influencing CYP3A4 and CYP2D6 activity prior to and during the study
3. Poor or ultra-rapid CYP2D6 metabolizer discovered on genotype screening

Date of first enrolment
15/12/2014

Date of final enrolment
20/05/2015

Locations

Countries of recruitment
Netherlands

Study participating centre
Centre for Human Drug Research
Zernikedreef 8
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Sponsor information

Organisation
Centre for Human Drug Research

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Sponsor type
Research organisation

Website
chdr.nl

ROR
https://ror.org/044hshx49

Funder(s)

Funder type
Industry

Funder Name
Heptares Therapeutics Ltd.

Results and Publications

Publication and dissemination plan
Clinical study report with all results (finalized in 2019). Scientific article to be published in peer-reviewed international pharmacological journal (due in 2020).

Intention to publish date
15/05/2020

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Not provided at time of registration