A Two Part Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics of SBT-020 in Patients with Early Stage Huntington*s Disease.

Published: 09-01-2017
Last updated: 14-04-2024

Part 1:Primary Objective- To assess the safety and tolerability of SBT-020 in early stage HD patients. Secondary Objective- To investigate the effect of SBT-020 on mitochondrial function, measured by dynamic 31P-MRS in calf muscles of early stage HD...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON45299

Source
ToetsingOnline

Brief title
SBT-020 in HD

Condition

- Movement disorders (incl parkinsonism)

Synonym
Early Stage Huntington□s Disease

Research involving
Human

Sponsors and support

Primary sponsor: Stealth Bio Therapeutics Inc
Source(s) of monetary or material Support: Stealth Bio Therapeutics Inc.

Intervention

Keyword: Huntington's disease, SBT-020

Outcome measures

Primary outcome

Tolerability / safety endpoints

- AEs leading to premature discontinuation of study drug.

- Treatment-emergent (S)AEs up to 5 pharmacokinetic half-lives after study drug discontinuation.

- Change from baseline to End-of-Study in vital signs: blood pressure and heart rate.

- Treatment-emergent ECG abnormalities up to 5 pharmacokinetic half-lives after study drug discontinuation.

- Treatment-emergent marked laboratory abnormalities up to 5 pharmacokinetic half-lives after study drug discontinuation.

Pharmacokinetic endpoints

Part 1:

- Plasma SBT-020 concentration.

Part 2:

- Plasma SBT-020 concentration.

Pharmacodynamic endpoints

- Mitochondrial function by 31P-MRS

o Phosphocreatine recovery time (in seconds), measured by 31P-MRS in calf muscles

o Difference between Pi/PCr ratio before, during and after visual stimulation, measured by 31P-MRS in the brain

- Intensity of red-green fluorescence, measured by flow-cytometry in PBMCs

- Various exploratory plasma and urinary biomarkers for mitochondrial function

- Neuropsychological assessments (only included in part 2)

o total number of correct responses in 90 seconds on the Symbol Digit Modality Test (SDMT)

o total number of correct responses in 45 seconds per trial on the Stroop colour word interference test

o completion time in seconds and number of errors for each trial on the Trail Making Test (TMT)

o total number correct on the Visual Verbal Learning Test (VVLT)

o the total number of (commission and omission) errors and the mean reaction time of all correct response trials on the Sustained Attention to Response Task (SART) test

o average performance (%) on the Adaptive Tracking task

- Motor function (only done during part 2)

o total motor score (TMS) (range 0-124) on the UHDRS

o total functional capacity score (TFC) score (range 0-13) on the UHDRS

o mean tapping rate and standard deviation on the Finger tapping test

o saccadic reaction time (seconds), saccadic peak velocity (degrees/second), saccadic inaccuracy (%) on the Saccadic eye movements test

o percentage of time the eyes are in smooth pursuit of the target (%) on the

Smooth pursuit test

o antero-posterior sway (in mm) on the Bodysway test

Secondary outcome

Not Applicable

Study description

Background summary

Huntington*s disease (HD) is an autosomal dominant inherited neurodegenerative disorder characterized by a triad of symptoms including motor disturbances, cognitive dysfunction and psychiatric symptoms (1-3). There is strong evidence that mitochondrial dysfunction is part of the pathogenesis of HD. Pharmacologically inhibiting succinate dehydrogenase in rodent and primates, thereby inhibiting complex II of the mitochondrial electron transport chain, resulted in pathology and symptomatology resembling HD (4, 5). Furthermore, in vitro research has shown that mutant huntingtin inhibits the import of nuclear coded mitochondrial proteins and down regulates the activity of peroxisome-activated receptor gamma (PPAR*), required for mitochondrial biogenesis (6). Using dynamic in vivo 31 phosphorus Magnetic Resonance Spectroscopy (31P-MRS) in the calf muscles it has been shown that HD patients exhibit a prolonged phosphocreatine recovery time (*PCr) compared to healthy controls, which can be translated into a reduduced mitochondrial function in HD patients (7, 8). Mitochondrial function in HD patients might therefore be beneficial for the disease progression by maintaining the energy level inside the striatum cells and thus preventing cell death. SBT-020 is an experimental mitochondrial function enhancing agent, which has showed promising results in pre-clinical animal models. While the exact mechanism of action is not completely understood, it is hypothesized that the compound can improve the mitochondrial function in HD patients, thereby slowing neuronal degeneration and disease progression.

Study objective

Part 1:
Primary Objective
- To assess the safety and tolerability of SBT-020 in early stage HD patients.
Secondary Objective
- To investigate the effect of SBT-020 on mitochondrial function, measured by

dynamic 31P-MRS in calf muscles of early stage HD patients.
- To assess the pharmacokinetics of SBT-020 in plasma in early stage HD patients.
- To assess the pharmacokinetics of SBT-020 (and SBT-020-related components) in urine in early stage HD patients.
- To investigate the effect of SBT-020 on mitochondrial function, by measuring the mitochondrial membrane potential (MMP) in isolated peripheral blood mononuclear cells (PBMCs).

Part 2:
Primary Objective
- To assess the safety and tolerability of longer term treatment with SBT-020 in early stage HD patients.
Secondary Objective
- To investigate the effect of SBT-020 on mitochondrial function, measured by dynamic 31P-MRS in calf muscles of early stage HD patients.
- To investigate the effect of SBT-020 on bioenergetic profile, measured by 31P-MRS in the brain of early stage HD patients.
- To assess the plasma concentration of SBT-020 in plasma in early stage HD patients.
- To investigate the effect of SBT-020 on mitochondrial function, by measuring the MMP in PBMCs.
- To investigate the effect of SBT-020 on an exploratory set of urinary and plasma biomarkers related to mitochondrial function in early stage HD patients.
- To investigate effects of SBT-020 on cognition and other CNS functions, using the NeuroCart test battery.
- To investigate effects of SBT-020 on motor functioning, using the NeuroCart test battery and unified Huntington*s disease rating scale.

Study design

- Part 1: A randomized, double-blind, placebo-controlled, repeat dose study of SBT-020 administered subcutaneously for 7 Days
- Part 2: A randomized, double-blind, placebo-controlled, repeat dose study of SBT-020 administered subcutaneously for 28 Days

Intervention

SBT-020 or placebo subcutaneously

Study burden and risks

As shown the first in man study, single and multiple doses of SBT-020 were generally safe and well tolerated at all dose levels when administered by SC injection to healthy male and female subjects. There were no serious or severe IMP-related AEs recorded during the study; 3 subjects were withdrawn as a

result of unrelated AEs. Overall, the incidence of AEs was low in Part 1 and slightly higher in Part 2; with injection site reactions reported most frequently. The current study will establish safety and PK data in the target population, therefore being the first step into bringing forth the first medical intervention in Huntington*s Disease. With the chosen methods (i.e. 31P-MRS) the proof of pharmacology of SBT-020 could be established, thus showing the ability to improve mitochondrial function and expanding the range of target populations.

Contacts

Public
Stealth Bio Therapeutics Inc

275 Grove Street 3-107
Newton MA 02466
US
Scientific
Stealth Bio Therapeutics Inc

275 Grove Street 3-107
Newton MA 02466
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female patient with a DNA confirmed diagnosis (CAG expansion of 36 or more repeats in the HTT gene) of HD

2. At least 18 years of age
3. Unified Huntington*s Disease Rating Scale (UHDRS) Total Motor Score (TMS) of 5 or more
4. Unified Huntington*s Disease Rating Scale (UHDRS) Total Functional Capacity Score (TFC) of 7 or more
5. tPCr of at least 32.4 seconds, measured by dynamic 31P-MRS of the calf muscles.
6. Absence of evidence of any significant active or chronic disease (apart from HD), following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, haematology, blood chemistry, and urinalysis, that might interfere with the study activities or patient*s safety by participating in the study, as judged by the investigator. Psychiatric comorbidities to HD (such as a major depressive disorder), are allowed under the scrutiny of the investigator.
7. Agrees to refrain from making any new, major life-style changes (e.g. starting a new diet or changing their exercise pattern)
8. Must agree to use adequate methods of contraception. Female subjects of childbearing potential must use two adequate forms of contraception, one of which must be a barrier method for the duration of the study and for 30 days after the last dose. Male subjects with a partner of childbearing potential must use two adequate forms of contraception, one of which must be a barrier method, for the duration of the study and for 30 days after the last dose.
9. Able to participate and willing to give written informed consent and to comply with the study restrictions.

Exclusion criteria

1. Positive test for drugs of abuse, such as metamphetamines and cocaine, at screening or pre-dose, except those prescribed by a physician for treatment of intercurrent medical issues due to HD.
2. History (within 3 months of screening) of alcohol consumption exceeding 2 standard drinks per day on average. Alcohol consumption will be prohibited during study confinement and at least 24 hours before screening and before each scheduled visit.
3. History of active malignancy within the last 5 years, with the exception of localized or in situ carcinoma (e.g., skin basal or squamous cell carcinoma).
4. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
5. Aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT) or total bilirubin levels >1.5 times the upper limit of normal at screening.
6. eGFR < 60 mL/min (calculated by the Modification of Diet in Renal Disease equation) at Screening.
7. Clinically significant abnormalities, as judged by the Investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the 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 HD patients.
8. Participation in an investigational drug or device study within 3 months prior to screening.
9. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening.

10. 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.
11. Presence of any contraindication to have MRI scans performed (e.g. claustrophobia, pacemaker, vascular clips etc.). MRI contraindications for both the 7 Tesla (part 1 and 2) and 3 T (part 2 only) MRIs will be assessed, using MRI contra-indications questionnaires and, if necessary, a plain radiograph.
12. Unwillingness to refrain from smoking more than half pack cigarettes per day (i.e. 10 units).
13. Specific cardiac abnormalities on the resting ECG at screening: QTcF> 450 or < 300 msec, evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker.
14. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
15. Unwillingness or inability to comply with the study protocol for any other reason.

Study design

Design

Study phase:	2
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):	03-03-2017
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	SBT-020
Generic name:	Not applicable

Ethics review

Approved WMO Date:	09-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-02-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-05-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-05-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-10-2017
Application type:	Amendment
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	EUCTR2016-003730-25-NL
CCMO	NL59198.056.16