A Phase 1 Study to Evaluate the Safety, Tolerability, and Immunogenicity of UBITh® PD Immunotherapeutic Vaccine (UB-312) in Healthy Participants and Participants with Parkinson*s Disease

Published: 11-06-2019
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Primary Objectives: 1. To evaluate the safety and tolerability of UB-312. 2. To evaluate the immunogenicity of UB-312 as determined by anti-alpha-synuclein (anti-aSyn) antibodies in blood and cerebrospinal fluid (CSF).

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

Summary

ID

NL-OMON54871

Source
ToetsingOnline

Brief title
Safety, Tolerability, and Immunogenicity of UB-312 in HV and PD patients

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: United Neuroscience (Subsidiary of Vaxxinity)
Source(s) of monetary or material Support: Pharmaceutical company

Intervention

Keyword: Immunogenicity, Parkinson's disease, UB-312, Vaccine

Outcome measures

Primary outcome

Primary Outcome Measures

Safety and tolerability will be assessed by adverse events (AEs), clinical

laboratory assessments, vital signs, neurological and physical examinations,

electrocardiograms (ECG), and safety MRI if applicable.

Immunogenicity will be measured by change from baseline of blood and CSF

anti-aSyn antibody titers.

Secondary outcome

N.A. Only primary and exploratory end points.

Study description

Background summary

It is estimated that 7 to 10 million people worldwide are living with PD (Parkinson*s News Today 2018). Parkinson*s disease evolves over many years with deterioration of motor, cognitive, behavioural and autonomic functions due to the progressive loss of synaptic function and neuronal death. The slow demise of dopaminergic, cholinergic, adrenergic, serotonergic and other synapses contributes to the spectrum of signs and symptoms in PD (Buddhala 2015). Although the mechanisms responsible for the dopaminergic cell loss in PD are not fully elucidated, one histological hallmark is the Lewy body which is formed from the fibrillar aggregation of alpha-synuclein (aSyn) (Baba 1998).

A key target for disease modification therapy in PD is the aggregated form of

aSyn, which is believed to initiate and propagate PD neuropathology. Fibrillar aggregates of aSyn are seen in the hallmark Lewy body lesions and in synapses and dendrites of PD brains at autopsy. Oligomeric aSyn aggregates are also found extracellularly in brains from PD cases and experimental models have shown that these can spread in the nervous system in a *prion-like* fashion to seed and propagate damage in PD relevant brain circuits (Marques 2012). Several companies are pursuing the aSyn aggregation neuronal injury cascade through therapeutic modalities such as monoclonal antibodies (mAbs), antisense oligonucleotides, and gene therapy. However, even if shown to be effective, a major concern with such therapies is their huge cost to the healthcare system and inaccessibility by most patients suffering from PD around the world. Thus, a pragmatic public health solution for PD remains elusive. The vaccination being investigated in this study could offer a solution.

Study objective

Primary Objectives:
1. To evaluate the safety and tolerability of UB-312.
2. To evaluate the immunogenicity of UB-312 as determined by anti-alpha-synuclein (anti-aSyn) antibodies in blood and cerebrospinal fluid (CSF).

Study design

This is a two-part randomized, double-blind, placebo-controlled study. Part A of the study with healthy participants will consist of dose escalation and cohort staggering for up to 7 planned dose levels or placebo. Part B of the study with PD participants will begin after interim analysis review of data collected during Part A, once all Part A participants complete assessments at Week 21 and the optimal dose(s) is selected based on safety, tolerability and immunogenicity of UB-312. All eligible participants will be enrolled in a 44-week study consisting of 20 weeks of treatment and 24 weeks of follow-up and undergo assessments as outlined in the Schedule of Assessments.

Intervention

UBITh® PD Immunotherapeutic Vaccine (UB-312)

Study burden and risks

No studies with UB-312 have been conducted in humans. To assess any potential impact with regard to safety, the investigator must refer to the Investigator*s Brochure for detailed information regarding warnings, precautions, contraindications, adverse events (AEs), and other significant data pertaining to the investigational product (IP) being used in this study.

Study procedure-associated risks for blood and cerebrospinal fluid (CSF) sampling, MRI and DaTscan imaging are described in the Informed Consent Form.

There are no expected benefits for healthy participants. The expected pharmacological actions of UB-312 are to elicit an antibody response against the pathological forms of aSyn, block its cell-to-cell spreading, attenuate aggregate formation, and facilitate the clearance of aSyn aggregates, resulting in a long-term protective effect against the neurotoxicity of aSyn. UB-312 is expected to improve motor, cognitive, and affective disabilities in alpha synucleinopathies, including PD.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Participants may be included in the clinical trial only if they meet all of the following criteria:
1. Written informed consent is signed and dated by the participant
2. Male or female aged 40 to 85 years old, inclusive at screening
3. Participants must have a body mass index (BMI) between 18 and 32 kg/m2, inclusive at screening, and with a minimum weight of 50 kg
4. Expected to be able to undergo all study procedures
5. Women must be of non-childbearing potential (postmenopausal for at least 12 months prior to screening or surgically sterile documented) or if of child-bearing potential, must be using medically acceptable contraceptive measures throughout the duration of the study and for at least 56 weeks after their last dose of study treatment.
6. Male participants and their partners of childbearing potential must commit to the use of medically acceptable contraception for the study duration and for at least 90 days after their last dose of study treatment. Men must refrain from donating sperm during this same period. The female partners should be asked to use a contraception method that is medically acceptable, and these contraceptive measures should be used throughout the duration of the study and for at least 90 days after their last dose of study treatment.

For Part B only:
7. A diagnosis of PD, confirmed by a neurologist
8. Hoehn & Yahr Stage <= III at Screening
9. Stable treatment of permitted antiparkinsonian medications from 30 days prior to first study drug administration or 60 days for MAO-B inhibitors, and expected to remain stable throughout the study unless required adjustment or initiation per the investigator*s judgement, except for short-acting rescue medications, which are allowed (see Section 7.1.1 for the list of permitted medications).
10. For participants that will need a DaTscan: must be willing and able from a medical standpoint to withhold medication that might interfere with dopamine transporter SPECT imaging (Neuroleptics, metoclopramide, alpha methyldopa, methylphenidate, reserpine, or amphetamine derivative) for at least 5 half-lives prior to screening DaTscan imaging

Exclusion criteria

Participants will be excluded from the clinical trial for any of the following reasons:
1. Clinically significant abnormalities, as judged by the investigator, in test results (including hepatic and renal panels, complete blood count, chemistry panel, urinalysis and imaging). 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.
2. History of medical, neurological or psychiatric conditions, which in the opinion of the investigator may compromise participant*s safety or scientific value of the study, posing an unacceptable risk to the participant or interfere with the participant's ability to comply with study procedures or abide by study restrictions.
3. History of Substance Use Disorder within the past 2 years before screening (Diagnostic and Statistical Manual of Mental Disorders-5 [DSM-V] criteria) or confirmed drugs of abuse or alcohol at Screening. Positive urine drug screen for prescribed medication is allowed at the discretion of the PI.
4. Acute or chronic infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV) at Screening, or any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV-1, HIV-2 infection, cytotoxic therapy in the previous 5 years.
5. History or evidence of an autoimmune disorder (e.g. Sjogren*s syndrome, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis etc.), which in the opinion of the investigator may compromise patient*s safety or scientific value of the study, posing an unacceptable risk to the participant.
6. Level of anti-cyclic citrullinated peptide (anti-CCP) above upper limit of normal at Screening.
7. Positive antinuclear antibodies (ANA) except judged to be clinically irrelevant by the investigator.
8. History of anergy.
9. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug or vaccine, or multiple drug allergies (non-active hay fever is acceptable).
10. History of cancer (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved) which has not been in remission for at least 5 years prior to Screening.
11. Clinically significant abnormal ECG or blood pressure measurement at screening or before the first dosing, as judged by the Investigator.
12. Contraindication to MRI, including but not limited to the presence of metal devices or implants (e.g. pacemaker, vascular- or heart-valves, stents, clips), metal deposited in the body (e.g. bullets or shells), or metal grains in the eyes.
13. Receipt of an investigational product or device, or participation in a drug research study within a period of 90 days before baseline at V1.
14. Participated/participating in any clinical trial with monoclonal antibodies or vaccines directed against aSyn.
15. Underwent any procedures/studies involving intracranial surgery, implantation of a device into the brain or stem cell study.
16. Pregnancy confirmed by a positive pregnancy test.
17. Participants who are currently breastfeeding, intend to breastfeed during the study or are planning to get pregnant and breastfeed within 56 weeks after last injection.
18. Use of any prohibited medications within 30 days or 5 half-lives (whichever

is greater) prior to Screening till end of treatment period; administration of chronic (defined as more than 14 days) immunosuppressants or other immune-modifying drugs within 6 months of Screening (including prednisone or equivalent, greater than or equal to 0.5 mg/kg/day; except intranasal, inhalation, and topical steroids which are allowed).
19. Vaccination within 30 days prior to Screening till end of treatment period unless approved by the Sponsor or its designees.
20. Any contraindication to undergoing a lumbar puncture (e.g., anatomical variations or local skin infection), as judged by the investigator.
21. Loss or donation of blood over 500 mL within three months prior to Screening or intention to donate blood or blood products for transfusion during the study and for 13 months after their last dose.
22. Received blood and/or blood derivatives treatment within 3 months prior to Screening.

For Part B only:
23. Positive test result for SARS-CoV-2 infection (if test performed according to local guidelines) in the 2 weeks prior to first dose.
24. Other known or suspected cause of Parkinsonism other than idiopathic PD, including but not limited to, progressive supranuclear gaze palsy, drug- or toxin-induced parkinsonism, essential tremor, primary dystonia, vascular parkinsonism.
25. Clinically significant neurological disease other than PD, such as multi-infarct dementia, Huntington's disease, normal-pressure hydrocephalus, brain tumor, progressive supranuclear palsy, multiple sclerosis, or history of significant head trauma followed by persistent neurologic defaults.
26. History or evidence at Screening of PD-related freezing episodes, falls, or clinically significant orthostatic hypotension, that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the participant in the opinion of the investigator.
27. Dopamine transporter single-photon emission computerized tomography scan (DaTscan) inconsistent with dopamine transporter deficit.
28. For participants that will need a DaTscan: current or recent (< 12 months) participation in studies or procedures involving exposure to ionizing radiation or radioactively labelled drugs/substances.

Study design

Design

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):	29-08-2019
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	11-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	19-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-11-2021
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	EUCTR2019-000688-26-NL
ClinicalTrials.gov	NCT04075318
CCMO	NL69891.056.19