CLINICAL TRIAL PROTOCOL

Investigational Product:
UBITh® PD Immunotherapeutic Vaccine (UB-312)

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

Protocol Number: UB-312-101	***Confidential***	Version: 6.0 Date: 14 APRIL 2022

1 Synopsis

Protocol Number	UB-312-101
Title	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.
Study Sites	CHDR, Leiden, the Netherlands LUMC, Leiden, the Netherlands (MRI and DaTscan only)
Study Description	This is a 44-week, randomized, placebo-controlled, double-blind, single-center, Phase 1 clinical trial consisting of a dose-escalation Part A study in healthy participants, followed by a Part B in participants with Parkinson's disease (PD) with selected doses from Part A.
Study Objectives	**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).
Outcome Measures	**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. **Exploratory Outcome Measures** Exploratory outcome measures may include but are not limited to the following: • Antibodies against different molecular forms of aSyn such as monomers, oligomers and fibrils • Antibodies against components of the vaccine, such as CpG1 and UBITh1 • Total and free aSyn concentrations in blood and CSF • T-cell ELISpot specific for the immunizing peptide (UB-312), the carrier (UBITh1), and the target (aSyn epitope) • For Part B only, exploratory clinical efficacy and safety assessments based on the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS, Parts II and III) and Montreal Cognitive Assessment (MoCA) • For Part B only - Biomarker-based target engagement will be measured by detecting misfolded aSyn in pre- and post-immunization CSF samples of PD patients using the protein misfolding cyclic amplification (PMCA) assay
Phase	1
Study Population	Eligible males and females, aged 40 to 85 years, inclusive at screening. For Part B only, participants with a diagnosis of Parkinson's Disease confirmed by a neurologist, and who present in Hoehn &Yahr Stages ≤ III.
Total Expected Number of Participants	Approximately 50 healthy participants (8 participants in the lowest dose cohort and 7 participants per cohort for ascending cohorts) and approximately 20 participants with clinically established PD will be enrolled to receive UB-312 treatment or matching placebo.

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 (Table 1). **Screening Phase (Part A and Part B):** After providing informed consent, participants will undergo screening assessments to determine eligibility to participate. All screening assessments are to be completed within 6 weeks prior to randomization at Visit 1. **Treatment Phase (Part A):** Eligible healthy participants will be enrolled into one of the 7 treatment cohorts. The first/lowest dose cohort (40 µg) will comprise 8 participants, randomized 6 active:2 placebo. The remaining cohorts will comprise 7 participants, randomized 6 active:1 placebo. The treatment arms are as follows: • Participants assigned to Cohort 1 will receive 40 µg UB-312 or matching placebo (0.2 mL) at Week 1, Week 5 and Week 13. • Participants assigned to Cohort 2 will receive 100 µg UB-312 or matching placebo (0.5 mL) at Week 1, Week 5 and Week 13. • Participants assigned to Cohort 3 will receive 1 dose of 40 µg UB-312 or matching placebo (0.2 mL) at Week 1, followed by 300 µg UB-312 or matching placebo (0.3 mL) at Week 5 and Week 13. • Participants assigned to Cohort 4 will receive 300 µg UB-312 or matching placebo (0.3 mL) at Week 1, Week 5 and Week 13. • Participants assigned to Cohort 5 will receive 1 dose of 40 µg UB-312 or matching placebo (0.2 mL) at Week 1, followed by 1000 µg UB-312 or matching placebo (1 mL) at Week 5 and Week 13. • Participants assigned to Cohort 6 will receive 1000 µg UB-312 or matching placebo (1 mL) at Week 1, Week 5 and Week 13. • Participants assigned to Cohort 7 will receive 2000 µg UB-312 or matching placebo (2 mL) at Week 1, Week 5 and Week 13. Dosing of cohorts will be staggered for safety. The first 2 participants (1 active and 1 placebo) enrolled into Cohort 1 will be observed for 24 hours at the study site to ensure there are no serious acute reactions prior to dosing of the remaining participants within the cohort. Once all participants within a cohort have been observed for 1 week following their first dose of study medication, available safety data will be reviewed before progressing to the next higher dose cohort. Cohorts 3 and 4 will be randomized and dosed concurrently, as will Cohorts 5 and 6. Participants in all cohorts will stay in the Clinical Research Unit approximately 6 hours after each dose, will have a phone call 24 hours after each dose and will have an onsite visit 1 week after each dose of study IP, to review for any injection site reactions and/or adverse events.

	Treatment Phase (Part B): Eligible PD participants will be enrolled into one of the 2 treatment cohorts. Each cohort will comprise 10 participants, randomized 7 active:3 placebo, where participants will receive 3 doses of UB-312 or placebo. The treatment arms are as follows: • Participants assigned to Cohort 8 will receive 300 µg UB-312 or matching placebo (0.3 mL) at Week 1, and 100 µg UB-312 or matching placebo (0.5 mL) at Week 5 and Week 13. • Participants assigned to Cohort 9 will receive 300 µg UB-312 or matching placebo (0.3 mL) at Week 1, Week 5 and Week 13. **Follow-up Phase (Part A and Part B):** All participants will be followed with blood collection at every 8 weeks until Week 45.
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/m^2, 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 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.

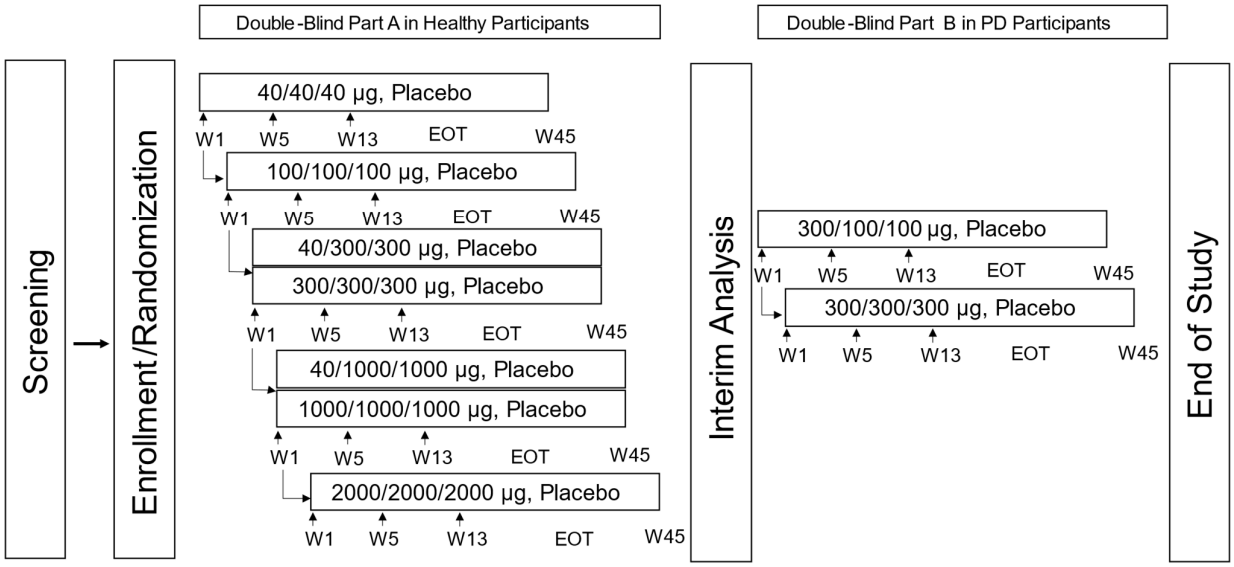
	11. Eligible participants must be fully vaccinated against COVID-19 according to local guidelines. Participants also must have received a COVID-19 booster vaccination, and the interval between booster vaccination and sample collection for inflammatory markers at Screening should be at least 7 days.
Exclusion 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 (other than the COVID-19 booster vaccination for Part B) till end of treatment period unless approved by the Sponsor or its designees. Participants in Part B will also be excluded if the COVID-19 booster vaccine was administered less than 7 days prior to collection of samples for inflammatory markers at Screening or less than 30 days prior to the first administration of study treatment. Regular vaccinations scheduled for preventative illnesses (e.g., flu, pneumonia) or additional COVID-19 booster vaccines required as per local guidelines after screening and during the treatment period need to be discussed with the Investigator and approved by the Sponsor or its designees on a case-by-case basis. 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.
Investigational Product	**UB-312** Drug Product is an UBITh®-linked synthetic peptide-based immunotherapeutic active vaccine mixed with CpG1 and Adjuphos. It is available in 100 µg or 500 µg per 0.5 mL dose per vial. **Placebo** is the delivery vehicle without UB-312 active peptides or CpG1, available in 0.5 mL dose per vial.
Participant Duration	Screening period: ≤ 6 weeks Treatment period: 20 weeks Follow-up period: 24 weeks
Sample Size Considerations	The sample size for Part A is not based on statistical considerations, but are considered adequate to initially characterize the safety and tolerability and dose response profile in UB-312 immunogenicity of increasing UB-312 doses in Part A. Although Part B is also exploratory by nature, a sample size of 10 subjects per dose group (7 active:3 placebo) was chosen taking into account the Part A serum anti-aSyn antibody titer results.
Statistical Considerations	Analysis will be performed at the end of the treatment phase and the end of the study. Summary statistics and plots will be generated for safety, immunogenicity and efficacy data, as deemed clinically appropriate. Incidence of AEs will be descriptively summarized. Other statistical considerations will be described in statistical sections and detailed in the Statistical Analysis Plan (SAP).

1.1 Study Schematic

Figure 1 Study Design Schematic



Interim analyses will be performed after all participants in Part A have completed Week 21/End of Treatment assessments.
EOT = End of Treatment; PD = Parkinson's Disease; W = Week; ✈ IP administration

Table 1 Study Schedule of Assessments

Visit	Screening	V1* Vaccination 1	V2	V3 Vaccination 2	V4	V5	V6 Vaccination 3	V7	V8	EOT or ET	Unscheduled Visit[15]	Follow-Up
Week	**Up to 6 weeks**	**1**	**2**	**5**	**6**	**9**	**13**	**14**	**17**	**21**	**N/A**	**29, 37, 45**
Day*	**-42 ~ 0**	**1[14]**	**8 (±1)**	**29[14] (±3)**	**36 (±3)**	**57 (±3)**	**85[14] (±3)**	**92 (±3)**	**113 (±3)**	**141 (±7)**	**N/A**	**197, 253, 309 (±7)**
Informed Consent	X											
Inclusion/exclusion criteria	X	X										
Medical history & demographics	X											
Medication review	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE review[1,2,3]		X	X	X	X	X	X	X	X	X	X	X
Vital signs[1,3,4]	X[1]	X[1]	X	X	X	X	X	X	X	X	X	X
Physical Exam[1,3,17]	X	X		X			X			X	X	X[18]
Neurological Exam[1,3,5]	X	X		X			X			X	X	X[18]
ECG[1,3,6]	X	X		X			X			X	X	
MRI		X[7]									X	
Randomization		X										
HIV, HCV, HBV test	X											
SARS-CoV-2 antigen test (when required)[22]	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[1,8]	X	X		X			X				X	
Clinical chemistry[1,9]	X	X		X			X		X	X	X	
Haematology[1,9]	X	X		X			X		X	X	X	
Coagulation[9]	X											
Urinalysis[1,9]	X	X		X			X		X	X	X	
Urine drug screen[1]	X	X									X	
Alcohol breath test[1]	X	X									X	
Inflammatory markers[1,10]	X	X		X			X			X	X	
Cytokines		X[20]		X[20]			X[20]			X	X[20]	
Antibodies in blood[1,9,16]		X	X	X	X	X	X	X	X	X	X	X

Visit	Screening	V1* Vaccination 1	V2	V3 Vaccination 2	V4	V5	V6 Vaccination 3	V7	V8	EOT or ET	Unscheduled Visit[15]	Follow-Up
Week	**Up to 6 weeks**	**1**	**2**	**5**	**6**	**9**	**13**	**14**	**17**	**21**	**N/A**	**29, 37, 45**
Day*	**-42 ~ 0**	**1[14]**	**8 (±1)**	**29[14] (±3)**	**36 (±3)**	**57 (±3)**	**85[14] (±3)**	**92 (±3)**	**113 (±3)**	**141 (±7)**	**N/A**	**197, 253, 309 (±7)**
Free and total aSyn[1]		X	X	X	X	X	X	X	X	X	X	X
ELISpot[1]		X							X	X[19]		
HLA typing[1]		X										
Blood collection for future research[1,11]		X	X	X	X	X	X	X	X	X	X	
CSF collection[1,21]		X								X	X	X[18]
Study Drug IM Injection		X		X			X					
Injection Site Reaction review[1,3]		X[14]	X	X[14]	X		X[14]	X			X	
For Part B only												
Hoehn and Yahr	X											
MDS-UPDRS (Parts II to III [1,12])		X								X	X	X[18]
DaTscan	X[8,13]											
MoCA		X								X		X[18]

AE=adverse event; CSF=cerebrospinal fluid; ECG=electrocardiogram; EOT = End of Treatment; ET = Early Termination; HBV = Hepatitis B virus; HCV=hepatitis C virus; HIV = human immunodeficiency virus; IM=intra-muscular; MDS-UPDRS=Movement Disorders Society – Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; MRI=magnetic resonance imaging; SAE=serious adverse event

* Time points for all visits are relative to Day 1 (day of first IMP administration). Every effort should be made to schedule visits as close as possible to the time point specified in the Schedule of Assessments. If a visit cannot be scheduled within the specified window, the timing of the visit and procedures should be discussed with the Sponsor.

1. Prior to administration of study IP at each applicable visit. Screening and V1 visits can be rescheduled if measured for moderate or severe illness and/or fever >38.0° Celsius within 1 week prior to visit.
2. AEs/SAEs recorded from time of informed consent up to and including Follow-up.
3. Also performed 45 minutes (+/- 15 minutes) and approximately 6 hours after administration of study IP at each applicable visit.
4. Including height (screening only); no need to repeat weight measurement for post-injection vital signs.
5. Full neurological exam at screening and last FU visit, brief neurological examination at other visits.
6. ECG in triplicate.
7. MRI will be performed between Screening and baseline (V1). For participants who were screen failed and subsequently re-screened to accommodate deployment of the COVID-19 booster vaccination, the original MRI performed during the initial screening can be accepted provided it was performed within 90 days of the start of treatment (Day 1).
8. For females of childbearing potential only, blood pregnancy test at screening and urine test at other visits. For part B, a urine pregnancy test will also be performed prior to DaTscan (in addition to the blood pregnancy test).
9. Specific measurements are listed in Section 10.6 of the protocol. Hematology and chemistry results will be available prior to the first study drug administration.
10. Inflammatory measures in blood will include: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR). At Screening only: antinuclear antibody (ANA), IgM rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). CRP level results will be available prior to study drug administration at each applicable visit. For participants who have undergone COVID-19 booster vaccination, inflammatory markers at Screening may be repeated if results at Screening are not within acceptable limits as required by the protocol.
11. Additional blood samples will be collected for future medical research in participants who consent.
12. Hoehn & Yahr for Screening only.
13. Historic DaTscan is acceptable.
14. Participants will stay for 6 hours after injection for safety observation. Participants will have a 24-hour telephone call. Daily injection site review and temperature recording will be done at home by the participant for 6 days, starting from the day after study drug administration.
15. Individual tests will be performed at Investigator's discretion.
16. Antibody measures in blood, including but not limited to: anti-aSyn target epitope (monomers, oligomers and fibrils may be analysed), anti-UBITh, anti-CpG1.
17. Full physical examination at screening and last FU visit, brief physical examination during the other visits.
18. Performed at the last follow-up visit only.
19. Only performed if PBMC sample for ELISpot not collected at V8.
20. The pre-dose cytokine blood samples analysis for (Part A) will include: IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13 and TNF-α. The cytokine panel in Part B is based on the observed effects in Part A, and will include: IFN-γ, IL-2, IL-6, IL-8, TNF-α, IFN-α and CXCL 10. Part B cytokine blood samples will be collected pre-dose and approximately 6 hours post-dose at each applicable visit, only analysed at PI's discretion if clinically indicated, otherwise, will be analysed at the end of study.
21. Biomarker-based efficacy will be measured by detecting aSyn aggregates in pre- and post-immunization CSF samples of PD patients using the protein misfolding cyclic amplification (PMCA) assay.
22. SARS-CoV-2 antigen test will be performed only in case of symptoms possibly related to COVID-19 and/or in accordance with prevailing local guidelines as described in the COVID-19 risk assessment and mitigation strategies for Study UB-312-101 on file at the investigational site.