STATISTICAL ANALYSIS PLAN

FOR CHDR1853 CLINICAL STUDY REPORT AND INTERIM REPORT

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

Short Title:	Safety, Tolerability, and Immunogenicity of UB-312 in HVs and PD patients
Version:	2
Date:	01-May-2023
CHDR number:	CHDR1853
Sponsor number:	UB-312-101
EudraCT number:	2019-000688-26

DOCUMENT HISTORY

Study 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.

The following revisions were made to the statistical analysis plan:

Version	Date	Rationale
1.0	03-Jun-2020	Initial version
2.0	01-May-2023	Update to last version of protocol for part B

CONTACT DETAILS

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SIGNATURE PAGE

Study 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**

I acknowledge responsibility for this statistical analysis plan in accordance with CHDR's current procedures.

[redacted]
Statistician

[redacted] *Electronically signed by: [redacted]*
Reason: I am the Author
Date: May 3, 2023 11:45 GMT+2

Signature | Date (dd Mmm yyyy)

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TRIAL SITE STAFF

Centre for Human Drug Research

I approve this statistical analysis plan.

G.J. (Geert Jan) Groeneveld, MD, PhD
Principal Investigator

[redacted] *Electronically signed by: Professor GJ Groeneveld*
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P. Eijsvogel
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Signature | Date (dd Mmm yyyy)

SPONSOR

Vaxxinity, Inc

I approve this statistical analysis plan on behalf of the sponsor.

[redacted]
SVP, Data Science

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 01-May-2023 | 13:48:36 PDT
775AC1C8E14445F7B7EE30A3840209DC

01-May-2023 | 13:48:43 PDT

Signature | Date (dd Mmm yyyy)

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALAT	Alanine Amino Transaminase
ASAT	Aspartate Amino Transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomic Therapeutic Chemical
AUCf	Area under the concentration – time curve
AUC_{inf}	Area under the concentration – time curve from time zero to infinity
AUC_{last}	Area under the concentration – time curve from time zero to time of last measurable concentration
AUC_{tau}	Area under the concentration – time curve between consecutive dosing
AUR	Area under the response
BDR	Blind data review
BMI	Body Mass Index
BP	Blood Pressure
bpm	beats per minute
CHDR	Centre for Human Drug Research
C_{max}	Maximum concentration
CRF	Case Report Form
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
ECG	Electrocardiogram
ELISPOT	Enzyme-linked immune absorbent spot
EOT	End of treatment
ESR	Erythrocyte sedimentation rate
ET	Early termination
HLA	Human leukocyte antigen
HR	Heart Rate
hrs	hour(s)
IFN	Interferon
IL	Interleukin

IP	Investigational product
ISR	Injection site reaction
LOD	Limit of detection
LOQ	Limit of quantification
LSM	Least Squares Mean
Max	Maximum
MCH	Mean Cellular Haemoglobin
MCHC	Mean Cellular Haemoglobin Concentration
MDS-UPDRS	Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
min	Minutes
Min	Minimum
mITT	Modified Intention-to-Treat
MRI	Magnetic resonance imaging
n	number of observations
p.o.	per os / orally
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred term
RF	Rheumatoid factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TNF	Tumour necrosis factor
$t_{½}$	Terminal Elimination Half-life
t_{max}	Time to attain C_{max}
WHO	World Health Organization

1 BACKGROUND AND RATIONALE

1.1 Purpose of the statistical analysis plan

This statistical analysis plan (SAP) describes in detail the analyses and presentation of the primary and exploratory endpoints for the clinical study report (CSR) and Interim analyses.

1.1.1 Study Objectives

1.1.1.1 Primary objectives

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

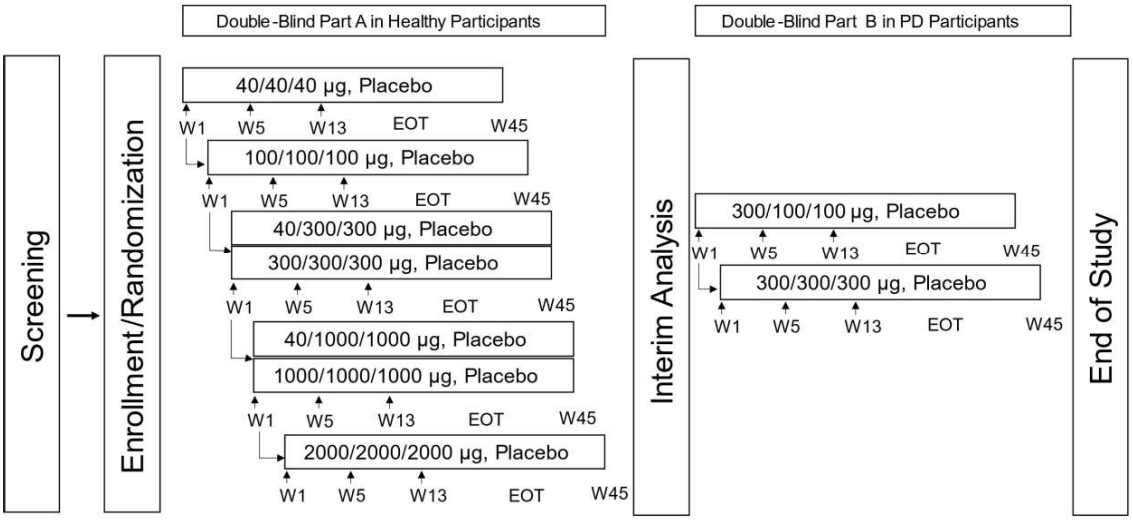
1.1.1.2 Exploratory objectives

To better understand:

- the immunogenicity of UB-312 against different molecular forms of aSyn;
- the immunogenicity against components of the vaccine;
- any differences in total and free aSyn concentrations in blood and CSF between the arms;
- any differences in motor aspects of experiences of daily living and motor examinations in PD participants.

1.2 Study Design

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

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 seven planned dose levels or placebo. After all participants of Part A complete the treatment phase of the study at Week 21, an interim analysis will be performed to select the dose for Part B, twocohorts with PD participants. This will be based on safety, tolerability and immunogenicity. All eligible participants will be enrolled in a 44-week study consisting of 20 weeks of treatment and 24 weeks of follow-up.

All assessments and timings are outlined in the Schedule of Assessments (**Appendix 1**).

1.3 Study documents

The following study documents were used for the preparation of the SAP:

SAP Version 1: Protocol CHDR1853 version 2.0, dated 17-Jun-2019.

SAP Version 2: Protocol CHDR1853 version 6.0, dated 14Apr2022

1.4 Study database

The following study database is used in the study:

- Investigator's (CRF) database, [redacted] v7.5

Data will be exported from [redacted] into a raw data ASCII file (.txt) and an accompanying SAS script will be generated by [redacted]. This SAS script will be used to read the raw data file and turn it into a SAS raw data file.

1.5 Requirements for SAP execution

The SAP will be finalized and signed off prior to database lock and study unblinding. The SAP, including programming of the tables, figures and listings, will be executed after:

- This SAP is signed-off;
- The database lock form is signed;
- The excluded subjects and data form is signed; and
- The database is locked (the [redacted] database is in the ANAlysis phase).

1.6 Statistical software & location

All safety and statistical programming is conducted with SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). Non-compartmental analysis is conducted with R 3.6.1 (or higher) for Windows (R Foundation for Statistical Computing, Vienna, Austria, 2019 (R Development Core Team, 2019) using the package PKNCA (version 0.9.1).

All the analysis data sets, programs and output will be stored in the study folders: PMX and PKPD (for non-compartmental analysis).

1.7 Validation of analysis dataset and reporting of programs

The final SAS data file used for the analysis will be compared with the SAS raw data file with a SAS procedure called “SAS compare”. This procedure will compare two data sets on the following features:

- Number of observations
- Number of variables
- Format and type of variables
- Variable values

The output of the SAS compare procedure is saved in a statistical data validation report. Statistical data validation reports are stored in the Stats/Analysis directory of the study. The validation report is checked by another statistician and signed by both the creator and the reviewer. The printed document is saved with the study files.

The final statistical report will include a section including 1) the unedited SAS analysis output and 2) the SAS scripts (syntax) used to generate the analysis.

1.8 Planned changes to endpoints or analyses from the protocol

1.8.1 Planned changes to endpoints

Not applicable.

1.8.2 Planned changes to analyses

Not applicable.

1.9 Sample size determination and total expected number of participants

The early phase clinical trial is exploratory in nature to assess the primary objectives of safety, tolerability, and immunogenicity of UB-312. Power calculations for comparison of adverse experience rates are too imprecise to be clinically meaningful because the actual rates are not even approximately known. The objective of evaluating the immunogenicity of UB-312 on anti-aSyn antibodies in cerebrospinal fluid will be an estimation, not a comparison. So, no power calculation is required.

Approximately 50 healthy participants (8 participants in the lowest dose cohort and 7 participants per cohort for ascending cohorts) and approximately 20 participants with PD will be enrolled to receive UB-312 treatment or matching placebo.

1.10 Randomization

The randomization code will be generated using SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) by a study-independent, CHDR statistician. Subjects will be randomized in a consecutive order starting with the lowest number. Participants will be numbered according to dosing group, e.g. subject will be numbered 1 to 8 in cohort 1, 9 to 15 in cohort 2, etc. Replacement subjects will be numbered +100, e.g. subject 5 will have subject 105 as replacement, and subject 105 will have subject 205 as replacement, etc. Participant replacement may be allowed if a participant was randomized but withdraws prior to administration of first dose. Dropouts after administration of first dose may be replaced after discussion between investigator and Sponsor.

The randomization code will be unblinded/broken and made available for data analysis only after study closure, i.e., when the study has been completed, the protocol deviations determined, and the clinical database declared complete, accurate and locked. The randomization code will be kept strictly confidential. Sealed individual randomization codes, per subject, will be placed in a sealed envelope, labelled 'emergency decoding envelopes' and will be kept in a safe cabinet at CHDR.

Healthy participants are assigned to one of the seven cohorts (Cohorts 1-7) in Part A: 8 participants to Cohort 1 (the lowest dose cohort) and 7 participants to each subsequent cohort. Twelve PD participants are assigned to Cohort 8 (Part B). All participants within a cohort are randomized to either UB-312 or placebo as indicated in the table below:

Cohort	UB-312	Placebo
1: First 2 Participants	N=1	N=1
1: 6 Other Participants	N=5	N=1
2, 3, 4, 5, 6, 7	N=6	N=1
8, 9	N=7	N=3

For Part A: Eligible participants will be randomized into one of the treatment cohorts:

Cohort	Week 1	Week 5	Week 13
1	40 µg (0.2 mL) or placebo	40 µg (0.2 mL) or placebo	40 µg (0.2 mL) or placebo
2	100 µg (0.5 mL) or placebo	100 µg (0.5 mL) or placebo	100 µg (0.5 mL) or placebo
3	40 µg (0.2 mL) or placebo	300 µg (0.3 mL) or placebo	300 µg (0.3 mL) or placebo
4	300 µg (0.3 mL) or placebo	300 µg (0.3 mL) or placebo	300 µg (0.3 mL) or placebo
5	40 µg (0.2 mL) or placebo	1000 µg (1 mL) or placebo	1000 µg (1 mL) or placebo
6	1000 µg (1 mL) or placebo	1000 µg (1 mL) or placebo	1000 µg (1 mL) or placebo
7	2000 µg (2 mL) or placebo	2000 µg (2 mL) or placebo	2000 µg (2 mL) or placebo

For Part B: dose(s) levels were selected based on interim analysis of safety, tolerability and immunogenicity data from all participants in Part A.

Cohort	Week 1	Week 5	Week 13
8	300 µg (0.3 mL), placebo	100 µg (0.5 mL), placebo	100 µg (0.5 mL), placebo
9	300 µg (0.3 mL), placebo	300 µg (0.3 mL), placebo	300 µg (0.3 mL), placebo

1.11 Interim analyses

1.11.1 Blinded safety review at the end of each cohort

Between each cohort in part A, blinded safety and tolerability data collected up to 7 days after the first dose of IP will be reviewed before escalating to the next cohort.

The following blinded safety data up to Day 8 will be reviewed by CHDR, sponsor and [redacted] medical monitor and used to determine if dose escalation can occur:

- Listing of AEs and SAEs
- Listing of concomitant medication
- Listings and spaghetti plots of vital signs, 12-lead ECG and inflammatory markers ESR and CRP

1.11.2 Interim analysis prior to Part B

A blinded interim analysis of immunogenicity, safety, and tolerability data up to Week 21 of all participants in Part A will be performed before the start of Part B, to determine the dosage(s) for the second part of this study. The review will include:

- Listing and summary tables of AEs and SAEs - including subject numbers
- Listing of concomitant medication - including subject numbers
- Listings, spaghetti plots and summary tables of vital signs and 12-lead ECG (the average of the triplicate ECGs will be used for ECG spaghetti plots and summary tables, as explained in 3.1.2)
- Listings, spaghetti plots, summary tables and shift tables for clinical laboratory results (blood/urine) - including subject numbers
- Listing of physical and neurological examination abnormalities - including subject numbers
- Listing of HLA types - including subject numbers
- Spaghetti plots and summary tables of cytokine data* - blinded to subject numbers except subjects who were unblinded
- Listing of the total IgE, IgG, IgA (taken unscheduled only for cohort 3 and 4, both prior and ~6h after the 3rd vaccination) – including subject numbers
- Spaghetti plots and summary tables of Immunogenicity results: anti-aSyn antibodies**, anti-UBITH antibodies and anti-CpG1 antibodies (research-grade assays)*** - blinded to subject numbers except subjects who were unblinded
- Spaghetti plots and summary tables of epitope-specific (UBITH, aSyn) IgE antibodies (research-grade assays)** - blinded to subject numbers except subjects who were unblinded
- Spaghetti plots and summary tables of total aSyn**, as well as free aSyn*** levels
- Listings, spaghetti plots and summary table of T-cell ELISPOT data**** - blinded to subject numbers except subjects who were unblinded

* Provided by CHDR in a separate report, since data is kept separate from the [redacted] database until database lock and unblinding.

** Provided by [redacted] in a separate report

*** Provided by [redacted] in a separate report

**** Provided by [redacted] in a separate report.

1.11.3 End of Treatment Analysis in Part B

The analysis of the end of treatment for Part B will be performed when the last patients in Part B complete the EOT/ET visit for administrative purposes. An external statistical vendor is planned to performance the analyses and in house study team remains blinded. The study team will remain blinded to the treatment of individual patients until the end of the study.

2 STUDY ENDPOINTS

2.1 Demographics and Baseline Characteristics

The baseline value is defined as the last available value before the first injection of study drug. The following demographic and baseline disease characteristics will be collected.

Demographic characteristics are age (unit: years), gender (levels: male or female), height (unit: cm), body weight (unit: kg), Body Mass Index (BMI, unit: kg/m^2) and race (levels: White/Black or African American/Asian/American Indian or Alaska Native/Native Hawaiian or other Pacific Islander/Mixed/Other).

Disease characteristics are only applicable for Part B and defined as disease duration (unit: years), Hoehn and Yahr (H&Y) stage (unit: none) at screening and baseline scores of Unified Parkinson's Disease Rating Scale (unit: none).

Complete physical and neurological examination will be performed at screening and brief physical and neurological examination (changes in specific findings) will be performed during post-baseline visits.

Abnormalities in physical examinations will be collected for:

- abdomen (levels: Yes or No);
- breast (levels: Not Done, Yes, or No);
- central nervous system (levels: Yes or No);
- ear, nose, throat (levels: Yes or No);
- extremities (levels: Yes or No);
- eyes (levels: Yes or No);
- head neck (levels: Yes or No);
- heart (levels: Yes or No);
- lungs/thorax (levels: Yes or No);
- lymph nodes (levels: Yes or No);
- musculo-skeletal system (levels: Yes or No);
- psychiatric examination (levels: Yes or No);
- skin (levels: Yes or No);
- other body systems (levels: Yes or No).

Abnormalities in neurological examinations will be collected for:

- Abnormality in Romberg test (levels: Yes or No);
- Abnormality in Pupillary reaction to light (levels: Yes or No);
- Abnormality in ocular movement and vision fields (levels: Yes or No);
- Abnormality in finger-nose test with eyes closed (levels: Yes or No);
- Abnormality in Heel-to-shin test (levels: Yes or No);
- Abnormality in Dysdiadochokinesis: Subject to quickly put fingertips of finger II-IV one after the other on the tip of thumb (levels: Yes or No);
- Abnormality in Tandem-Walk: Stepping on a line on the floor with eyes open (levels: Yes or No);
- Abnormality in elbow and knee flexor or extensor strength or grip strength
- Abnormality in muscle stretch reflexes (levels: Yes or No);
- Abnormality in soft touch with cotton wool on all four extremities (levels: Yes or No);
- Any significant abnormalities on neurological examination (levels: Yes or No).

When there is an abnormality observed by the physician in any physical or neurological examination as above, s/he will report description about the abnormality as a free-text in the database.

Medical history data events collected at screening will consist of the following:

- any allergy for iodine, latex, any medication, plasters or any other;
- any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug or multiple drug allergies (non-active hay fever is acceptable);
- any symptoms associated with an autoimmune disorder (e.g. inflammation of joints, morning stiffness, inflammatory back pain, photosensitivity of the skin or other skin complaints, Raynaud phenomenon, alopecia, oral ulcers, sicca complaints, inflammation of the eyes, chronic gastro-intestinal diseases or chronic diarrhoea);
- receive any blood and/or blood derivatives treatment within 3 months prior to Screening;
- any 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;
- anergy (failure to initiate a full immune response against a vaccine);
- an autoimmune disorder (e.g. Sjogren's syndrome, systemic lupus erythematosus, rheumatic 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;
- disorders of cardiovascular, endocrine, gastrointestinal, head/eyes/nose/throat, haematological, hepatic, immunological, musculoskeletal, neurological, psychiatric, pulmonary, renal, sensory, dermatological, urogenital, or any other;
- relevant abnormalities in family history;
- any contraindication to undergoing a lumbar puncture (e.g. anatomical variations or local skin infection) as judged by the investigator;
- recent Illness;
- underwent any procedures/studies involving intracranial surgery implantation of a device into the brain or stem cell study.

Medical history is an event-based data and only collected if there has been any of above events reported at screening.

Lastly, previous and concomitant medication and inflammatory measures in blood such as antinuclear antibody and IgM rheumatoid factor will be collected at screening.

2.2 Safety and tolerability endpoints

- Treatment emergent AEs
- Serious treatment emergent AEs
- Treatment emergent AEs leading to treatment discontinuation
- Concomitant medication
- Physical and neurological examinations
- Clinical laboratory tests
  - Haematology
    - Haemoglobin (unit: mmol/L)
    - Haematocrit (unit: L/L)
  - Chemistry
    - Sodium (unit: mmol/L)
    - Potassium (unit: mmol/L)

- Erythrocytes (unit: 10E12/L)
- Mean Cellular Volume (MCV; unit: fL)
- Mean Cellular Haemoglobin (MCH; unit: fmol)
- Mean Cellular Haemoglobin Concentration (MCHC; unit: mmol/L)
- Leucocytes (unit: 10E9/L)
- Platelet count (unit: 10E9/L)
- Eosinophils (unit: 10E9/L)
- Basophils (unit: 10E9/L)
- Neutrophils (unit: 10E9/L)
- Lymphocytes (unit: 10E9/L)
- Monocytes (unit: 10E9/L)
- Urea (unit: mmol/L)
- Uric Acid (unit: mmol/L)
- Creatinine (unit: µmol/L)
- Total Bilirubin (unit: µmol/L)
- Conjugated Bilirubin (unit: µmol/L)
- Albumin (unit: g/L)
- Total Protein (unit: g/L)
- ASpartate Amino Transaminase (ASAT; unit: U/L)
- ALanine Amino Transaminase (ALAT; unit: U/L)
- Glucose (unit: mmol/L)
-

- Urinalysis
  - Bilirubin (levels: Negative, +, ++ and +++)
  - Blood (levels: Negative; Non-haemolyzed 10 ery/ul; Non-haemolyzed 80 ery/ul; Haemolyzed 10 ery/ul; 25 ery/ul; 80 ery/ul; 200 ery/ul)
  - Glucose (levels: Negative; 5.5 mmol/l; 14 mmol/l; 28 mmol/l; 55 mmol/l; ≥111 mmol/l)
  - Ketone (levels: Negative; 0.5 mmol/l; 1.5 mmol/l; 4 mmol/l; 8 mmol/l; 16 mmol/l)
  - Leucocytes (levels: Negative; 15 leuco/ul; 70 leuco/ul; 125 leuco/ul; 500 leuco/ul)
  - Nitrite (levels: Negative; Positive 1; Positive 2)
  - Protein (levels: Negative, trace, 0.30 g/l; 1 g/l; 3 g/l; ≥ 20 g/l)
  - Specific gravity (levels: 1.000, 1.005; 1.010; 1.015; 1.020; 1.025; 1.030)
  - Urobilinogen (levels: 3.2 µmol/l; 16 µmol/l; 33 µmol/l; 66 µmol/l; 131 µmol/l)
  - pH (levels: 5.0; 6.0; 6.5; 7.0; 7.5; 8.0; 8.5)
- Vital signs
  - Temperature (ºC)
  - Pulse Rate supine (unit: bpm)
  - Systolic BP supine (unit: mmHg)
  - Diastolic BP supine (unit: mmHg)
  - Respiratory rate (unit: br/minute)
- 12-Lead electrocardiogram (ECG)
  - Diagnosis
  - Heart Rate (HR) (unit: bpm)
  - PR interval (unit: msec)
  - QRS duration (unit: msec)
  - QT interval (unit: msec)
  - QTcF (unit: msec)

- Local tolerability at injection site
  - Diarrhoea (levels: No; Yes, 1-3 times; Yes, 4-6 times; Yes, >6 times)
  - Dizziness (levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
  - Fatigue (levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
  - Fever (levels: No, <38.0 ºC; Yes, 38.0-38.4 ºC; Yes, 38.5-38.9 ºC; Yes, 39.0-40.0 ºC; Yes, >40.0 ºC)
  - Hard knot at injection site (levels: No; Yes, <2.5 cm in diameter; Yes, 2.5-5 cm in diameter; Yes, 5.1-10 cm in diameter; Yes, >10 cm in diameter)
  - Headache (levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
  - Muscle pain (levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
  - Nausea/Vomiting (levels: No; Yes, 1-2 times; Yes, 3-4 times; Yes, >4 times)
  - Other abnormalities at injection site (levels: No or Yes)
  - Painfulness at injection site (levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
  - Physical discomfort (levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
  - Redness at injection site (levels: No; Yes, <2.5 cm in diameter; Yes, 2.5-5 cm in diameter; Yes, 5.1-10 cm in diameter; Yes, >10 cm in diameter)
  - Swelling at injection site (levels: No; Yes, <2.5 cm in diameter; Yes, 2.5-5 cm in diameter; Yes, 5.1-10 cm in diameter; Yes, >10 cm in diameter)
  - Tenderness at injection site (levels: No; Mild: Slightly uncomfortable when pressure; Moderate: Discomfort upon movement; Severe: Discomfort at rest)
- Participant-reported local tolerability at injection site and systemic complaints (eDiary app)
  - Painfulness at injection site in past 24 hours (Dia_Pain; levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
  - Tenderness at injection site in past 24 hours (Dia_Tender; levels: No; Mild: Slightly uncomfortable when pressure; Moderate: Discomfort upon movement; Severe: Discomfort at rest)
  - Redness at injection site in past 24 hours (Dia_Redness; levels: No; Yes, <2.5 cm in diameter; Yes, 2.5-5 cm in diameter; Yes, 5.1-10 cm in diameter; Yes, >10 cm in diameter)
  - Hard knot at injection site in past 24 hours (Dia_HardKnot; levels: No; Yes, <2.5 cm in diameter; Yes, 2.5-5 cm in diameter; Yes, 5.1-10 cm in diameter; Yes, >10 cm in diameter)
  - Swelling at injection site in past 24 hours (Dia_Swelling; levels: No; Yes, <2.5 cm in diameter; Yes, 2.5-5 cm in diameter; Yes, 5.1-10 cm in diameter; Yes, >10 cm in diameter)

- Fever in past 24 hours (Dia_Fever; levels: No, <38.0 ºC; Yes, 38.0-38.4 ºC; Yes, 38.5-38.9 ºC; Yes, 39.0-40.0 ºC; Yes, >40.0 ºC)
- Vomiting in past 24 hours (Dia_Vomit; levels: No; Yes, 1-2 times; Yes, 3-4 times; Yes, >4 times)
- Diarrhoea in the past 24 hours (Dia_Diarrhoe; levels: No; Yes, 1-3 times; Yes, 4-6 times; Yes, >6 times)
- Headache in past 24 hours (Dia_Headache; levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
- Dizziness in past 24 hours (Dia_Dizzines; levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
- More fatigue than normal in past 24 hours (Dia_Fatigue; levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
- Muscle pain in past 24 hours (Dia_MuscPain; levels: No; Mild: Does not interfere with daily life; Moderate: Interfere with daily life; Severe: Seriously hinder daily life)
- Other symptoms in past 24 hours (Dia_OtherSym; levels: No or Yes)
- Any changes in existing medication taken in the past 24 hours (MedChange; levels: Yes. Medication stopped; Yes. Medication dose changed; No; N/A. No medication used)
- Any new medication in the past 24 hours (NewMedicat; levels: Yes; No)

- Inflammatory blood parameters
  - C-Reactive protein (CRP, unit: mg/L) (CRP parameter is present in the database under two activities, namely BsCRP and BsChemCRP. Data from both will be combined)
  - ESR (unit: mm/hr)
  - Interferon-gamma (IFN-γ; pg/mL)
  - Interleukin 1-beta (IL-1β; pg/mL)
  - Interleukin 2 (IL-2; pg/mL)
  - Interleukin 4 (IL-4; pg/mL)
  - Interleukin 6 (IL-6; pg/mL)
  - Interleukin 8 (IL-8; pg/mL)
  - Interleukin 10 (IL-10; pg/mL)
  - Interleukin 12p70 (IL-12p70; pg/mL)
  - Interleukin 13 (IL-2; pg/mL)
  - Tumour necrosis factor-alfa (TNF-α; pg/mL)

2.3 Efficacy endpoints

Blood and CSF-based antibody variables are collected during baseline and post-baseline visits. Immunogenicity (level, C_{max}, t_{max}, $AUC_{0\text{-last}}$, half-life) will be based on the observed data:

- anti-aSyn antibody titers in serum and CSF
- anti-UBITH antibody titers in serum and CSF
- anti-CpG1 antibody titers in serum and CSF

The following antibody parameters will be derived by non-compartmental analysis of the serum anti-aSyn, and may be derived also for anti-UBITH and anti-CpG1 antibody titers - time profiles following the third study drug injection:

- C_{max}: Maximum titer level
- t_{max}: Time of maximum titer level (days after last injection)
- $AUC_{0\text{-last}}$: Area under the titer – time curve from time of last injection to time of last measurable level.
- $t_{1/2}$: Half-life (1/days)

Serum and CSF levels of antibodies targeting the carrier (UBITh1), CpG1, and different aSyn forms such as monomers, oligomers and fibrils may be measured during the study, and will be based on the observed and change from baseline data.

Free and total aSyn values will be measured during the study and will be based on the observed and change from baseline data.

For Part B Outcome Measures

MDS-UPDRS Parts II and III are rated at baseline, EOT/ET, and the last follow up visits. MDS-UPDRS Parts II and III sub scores and total scores will be based on the observed and change from baseline data.

MDS-UPDRS part II questionnaire consists of the following items:

- UPDRS part 2 Speech (MDS_201; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Saliva and drooling (MDS_202; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Chewing and swallowing (MDS_203; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Eating tasks (MDS_204; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Dressing (MDS_205; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Hygiene (MDS_206; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Handwriting (MDS_207; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Doing hobbies and other activities (MDS_208; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Turning in bed (MDS_209; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)

- UPDRS part 2 Tremor (MDS_210; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Getting out of bed, a car or a deep chair (MDS_211; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Walking and balance (MDS_212; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 2 Freezing (MDS_213; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)

MDS-UPDRS part III questionnaire consists of the following items:

- MDS-UPDRS 3a Medication use for patient's clinical state (MDS_3a; Numeric: 0, 1; Levels: No or Yes)
- MDS-UPDRS 3b Patient's clinical state on medication (MDS_3b; Numeric: 0, 1, 2; Levels: ON or OFF or N/A. No medication)
- MDS-UPDRS 3c On levodopa (MDS_3c; Numeric: 0, 1; Levels: No or Yes)
- UPDRS part 3 Speech (MDS_301; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Facial Expression (MDS_302; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Rigidity LLE (MDS_303_LLE; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Rigidity LUE (MDS_303_LUE; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Rigidity Neck (MDS_303_Neck; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Rigidity RLE (MDS_303_RLE; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Rigidity RUE (MDS_303_RUE; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Finger tapping – Left (MDS_304_L; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Finger tapping – Right (MDS_304_R; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Hand movements – Left (MDS_305_L; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Hand movements – Right (MDS_305_R; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Pronation-supination movement of hands – Left (MDS_306_L; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Pronation-supination movement hands – Right (MDS_306_R; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Toe tapping – Left (MDS_307_L; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Toe tapping – Right (MDS_307_R; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Leg agility – Left (MDS_308_L; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Leg agility – Right (MDS_308_R; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Arising from chair (MDS_309; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Gait (MDS_310; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)

- UPDRS part 3 Freezing of gait (MDS_311; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Postural stability (MDS_312; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Posture (MDS_313; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Global spontaneity of movement (MDS_314; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Postural tremor of the hands – Left (MDS_315_L; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Postural tremor of the hands – Right (MDS_315_R; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Kinetic tremor of the hand – Left (MDS_316_L; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Kinetic tremor of the hand – Right (MDS_316_R; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Rest tremor amplitude LLE (MDS_317_LLE; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Rest tremor amplitude LUE (MDS_317_LUE; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Rest tremor amplitude LipJaw (MDS_317_LipJ; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Rest tremor amplitude RLE (MDS_317_RLE; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Rest tremor amplitude RUE (MDS_317_RUE; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Constancy of rest tremor (MDS_318; Numeric: 0, 1, 2, 3, 4; Levels: Normal or Slight or Mild or Moderate or Severe)
- UPDRS part 3 Dyskinesia impact on part III ratings A (MDS_3DyskinA; Numeric: 0, 1; Levels: No or Yes)
- UPDRS part 3 Dyskinesia impact on part III ratings B (MDS_3DyskinB; Numeric: 0, 1, 2; Levels: No or Yes or NA(A=no))
- UPDRS part 3 Hoehn and Yahr stage (MDS_3DyskinB; Numeric: 0, 1, 2, 3, 4, 5; Levels: Asymptomatic or Unilateral involvement only or Bilateral involvement without balance impairment or Mild to moderate involvement or Severe disability or Wheelchair bound or bedridden)

MONTREAL COGNITIVE ASSESSMENT (MOCA)
MOCA score, and the change from baseline to end of treatment, and follow up visits will be summarized by treatments

3 DATA HANDLING

3.1 Derived variables

3.1.1 Body Mass Index

Body mass index will be derived at individual level using following derivation rule unless it is conducted automatically in the [redacted] database:

$$Body\ Mass\ Index = \frac{\text{Participant's weight in kg}}{(\text{Participant's height in meter})^2}$$

3.1.2 12-lead ECG replicates

Triplicate measurements are taken for each 12-lead ECG variable (e.g. HR, PR interval, QRS, QT and QTcF) with one-minute time interval. Those triplicate readings will be handled by calculating the average of the three measurements as follows:

$$Average\ ECG = \frac{(\text{1st reading of ECG parameter} + \text{2nd reading of ECG parameter} + \text{3rd reading of ECG parameter}}{3}$$

3.1.3 MDS-UPDRS part II and III total score (part B only)

MDS-UPDRS part II and part III total scores will be calculated by summing up the numerical results of the MDS-UPDRS part II and III questionnaire items. For part II, this is the sum of 18 ratings performed by the physician and for part III this is the sum of 13 questions.

3.1.4 Antibody Parameters

Values of the maximal concentration (C_{max}) and the time to reach C_{max} (t_{max}) are obtained directly from the individual anti-aSyn, anti-UBITH and anti-CpG1 antibody titer-time profiles. If the same maximum titer levels are observed at two or more time points, the earliest time point should be used as t_{max}.

For each individual antibody titer-time profiles the area under the curve from 0 to the last quantifiable observation ($AUC_{0\text{-last}}$) and the half-life will be calculated. The $AUC_{0\text{-last}}$ will be calculated using the linear trapezoidal rule. The half-life will be calculated as $t_{1/2}$=ln(2)/lambda_z, where lambda_z is the terminal elimination rate constant determined by unweighted least squares regression of the terminal part of each individual log/linear concentration-time profile. The following rules will be applied to determine the terminal elimination phase:

- The slope of the regression line must be negative (lambda_z>0).
- Sample at t_{max} cannot be included.
- At least 3 data points should be used.
- $R^2 > 0.85$

In general, the more data points that are used in the estimation, the better. The number of data points will be selected automatically to achieve the largest adjusted R^2 value. If two adjusted R^2 values (based on different number of data points) deviated with less than 0.0001, then the fit based on the most data points will be selected.

3.2 Handling of missing data

All missing or incomplete safety and efficacy data, including dates and times, are treated as such. Missing test results or assessments will not be imputed. Missing safety and efficacy data, indicated as 'M' in the data listing, will be assumed to be missing-at-random (MAR) when the statistical mixed model using SAS PROC MIXED is employed.

For graphical and summary purposes efficacy and safety values below the limit of quantification (LOQ; if applicable) will be set to half (½) of the LOQ. For analysis no undetermined values will be replaced, except pre-values below the LOD/LOQ that are used as covariate. They will be replaced by 50% of the LOD/LOQ.

For calculation of AUC_{last}, all titer levels below the LOQ will be set to half (½) of the LOQ. For calculation of half-life all levels below the LOQ will be treated as "missing".

If data points for antibody titers are missing, the AUC parameters will be derived by interpolating with regard to the two neighbouring non-missing values.

If the actual sampling time is missing, but a valid antibody value is measured, the scheduled protocol time will be used for the calculation of the antibody parameters.

3.3 Handling of outliers

The final efficacy analysis will be preceded by a blind data review (BDR) which consists of individual graphs per visit by time of all efficacy measurements. The graphs will be used to detect outliers and measurements unsuitable for analysis. All data points to be removed or changed before analysis will be noted and justified on the form "Excluded subjects and data" and this will be signed by the statistician and the principal investigator before database lock.

3.4 Handling of protocol deviations

Subjects with protocol deviations will not be excluded from the analyses of the safety data (except in the case of subjects with all post-baseline safety data missing); such subjects may be excluded from the analysis of the efficacy data at the discretion of the responsible statistician and principal investigator, blinded to treatment allocation (subjects not excluded are then referred to as the Per-Protocol population, see 4.1.3). This will also be noted on the form "Excluded subjects and data".

3.5 Assignment of preferred terms to original terminology

The original terms used by the investigator will be assigned preferred terms for classification and tabulation. The following dictionary databases will be used for assigning preferred terms:

- AEs/SAEs: MedDRA Version 21.1 or higher
- Previous/Concomitant Medications: WHO-ATC/WHO Drug B3 format of March 2019

3.6 Reporting conventions

P-values ≥0.0001 will be reported to 4 decimal places; P-values less than 0.0001 will be reported as "<0.0001". Upper case is used for P-value. The mean, standard deviation (SD), and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum (Min) and maximum (Max) will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures. Confidence limits (abbreviated CLs) will be separated by a hyphen, e.g., xxx - xxx).

Tables and listings are programmed following the following rules:

Final deliverable	Word 2010 document (docx)			
Page Option	Landscape		Portrait	
Courier New Font	Number of cols	Number of lines	Number of cols	Number of lines
8	150	45	100	70

Graphic outputs will be produced in png or emf format.

Subjects randomized to Placebo group at each cohort will be pooled and represented only one study group in any reporting outputs.

4 STATISTICAL METHODOLOGY AND ANALYSES

4.1 Analysis Sets

The analyses of immunogenicity and efficacy endpoints will be performed by the treatment allocation and based on the modified Intention-to-Treat (mITT) and Per-Protocol (PP) populations as defined below. If both populations are identical, results will only be presented for mITT population.

Safety endpoints and tolerability will be analysed based on the safety population as defined below.

4.1.1 Safety population

The safety population is the total treated population defined as all participants randomized and exposed to at least one dose of the study drug, regardless of the amount of treatment administered.

4.1.2 Modified Intention-to-Treat (mITT) population

Modified intention-to-treat (mITT) population consists of all randomized participants who receive at least one dose of the study drug and have both baseline and at least one post-baseline assessment in any of the primary or secondary variables, irrespective of compliance with the study protocol and procedures.

4.1.3 Per-Protocol (PP) population

Per-protocol (PP) population includes all participants who receive all planned doses of the study drug, complete the treatment period, fulfil all entry criteria, and have no critical or major protocol deviations (as described in Table 1 of Protocol Deviation Handling Plan) that requires exclusion of the participant. Prior to database lock, all protocol deviations will be determined and reviewed, and CHDR and UNS will jointly decide whether the deviations require a participant to be excluded from the efficacy analysis population.

4.2 Subject disposition

The following subject data will be listed by subject and summarized by study part:

- Screened participants: all participants who have signed the informed consent
- Randomized participants: participants who receive a randomization number
- The safety population
- The mITT population
- The PP population

For the following two categories of participants, counts, and percentages will be calculated for each treatment group using the number of randomized participants in each group as denominator.

- Participants who have completed the treatment period
- Participants who discontinued the study drug during the treatment period

A list of participants prematurely withdrawn from the study, along with reasons for discontinuation, will be provided. Reason for withdrawal will be tabulated using count and percentage of participants by treatment group and overall. A participant must be withdrawn from the study for any of the following reasons:

- Adverse event
- Screen failure
- Study terminated by sponsor
- Pregnancy

- Withdrawal by subject
- Lost to follow-up
- Physician decision
- Protocol deviation
- Death
- Other
- Reserve subject

4.3 Baseline characteristics

4.3.1 Demographics and baseline variables

Demographic and baseline disease characteristics data (only applicable for part B, being Hoehn & Yahr stage and disease duration) will be summarized by treatment group and overall for the safety population in each study part.

Continuous demographic and baseline disease characteristics (e.g., age, height, weight, BMI) will be summarized by using descriptive statistics (n, mean, SD, median, Min, Max).

Qualitative demographic characteristics (gender, race) will be summarized by counts and percentages.

Demographics data will also be listed. The listing will include subject number, date of inform consent, date of dosing, treatment, age of subject, gender, race, height, weight and BMI.

4.3.2 Medical and surgical history

Medical history will be listed and summarized.

Pathologies associated with past medical and surgical history will be classified into primary system organ classes and preferred terms using MedDRA (version 21.1 or higher) and will be summarized by treatment group and overall using counts and percentages.

4.3.3 Physical and neurological examinations

Physical and neurological examination abnormalities will only be listed. The listing for physical and neurological examinations will contain subject number, visit, examination date and time, body system and abnormalities.

4.3.4 Treatment tolerability and compliance

The overall treatment tolerability of UB-312 in each study part is defined as the percentage of number of administered UB-312 doses divided by number of administered UB-312 doses plus number of missed UB-312 doses of participant(s) who dropped out due to drug-related AE(s).

All administrations (date/time) will be listed by presenting subject number, visit, dose, volume of dose, injection completion.

4.4 Safety and tolerability endpoints

The safety set is used to perform all safety analyses.

Baseline is defined as the last value prior to first dosing. Change from baseline will be calculated for all continuous safety parameters.

4.4.1 Adverse events

The AE coding dictionary for this study will be Medical Dictionary for Regulatory Activities (MedDRA). It will be used to summarize AEs by primary system organ class (SOC) and preferred term (PT).

The observation period will be divided into 2 segments: pre-treatment and post-treatment.

- The pre-treatment period is defined as the time from the date of the informed consent to the time before the administration of first dose of study medication.

- The post-treatment period is defined as the time from after the first dose of study medication to the end of the study.

Pre-treatment AEs are defined as AEs that develop or worsen or become serious during the pre-treatment period.

Treatment-emergent AEs (TEAEs) are defined as AEs that develop or worsen (according to the investigator's judgement) or become serious during the post-treatment period.

The primary focus of adverse event reporting in the CSR will be TEAEs. Pre-treatment AEs will be described separately.

All AEs and SAEs will be displayed in listings. The listing will contain subject number, treatment, occasion, dosing date, SOC, PT, start date and time of AE, duration of AE, severity, SAE, relationship and chronicity.

Summaries of all TEAEs in each treatment group and overall (pooled Placebo versus pooled treatment groups), will include:

- The overview of AEs, summarizing number (%) of subjects with any TEAE/serious TEAE.
- The number and percentage of subjects with at least one TEAE by System-organ Class and Preferred Term.
- Summary of TEAEs by intensity (mild, moderate, severe, life-threatening, death), presented by System-organ Class and Preferred Term.
- Summary of TEAEs by causal relationship to the study drug, by System-organ Class and Preferred Term.

4.4.2 Previous and Concomitant Medications/Therapy

Previous and concomitant medications will be coded according to the World Health Organization (WHO) drug code and the anatomical therapeutic chemical (ATC) class code.

Medications will be classified into the following two groups:

- Previous medications are those that the participant took within the 30 days prior to the screening visit and prior to the first administration of the study drug at Week 1 (V1/baseline).
- Concomitant medications are those that the participant continued or started on or after the first injection of the study drug up to the end of the study.

These medications will be classified into anatomic and therapeutic classes using the World Health Organization (WHO) Drug Dictionary. Participants will only be counted once within each anatomic and therapeutic class.

Descriptive statistics including number of participants and percentage will be provided. No statistical testing for between-group difference will be performed.

All concomitant medications will be displayed in a listing. The listing will contain subject number, treatment, occasion, dosing date, start date and time of concomitant medication intake, duration, medication name, dose, regimen, route, and indication.

4.4.3 Physical and neurological examinations

Physical and neurological examination abnormalities (changes in specific findings compared to baseline) will only be listed. The listing for physical and neurological examinations will contain subject number, visit, examination date and time and abnormalities.

4.4.4 Vital signs

At each time point, absolute values and change from baseline of vital signs will be summarized by treatment group using descriptive statistics of n, mean, SD, SEM, median, Min, and Max values.

The number of available observations and out-of-range values (absolute and in percentage) will be listed. Values outside the reference range will be flagged in the listing. 'H' and 'L', denoting values above or below the investigator reference range (when present), will flag as out-of-range results in the listing.

4.4.5 12-lead ECG

At each time point, absolute values and change from baseline of ECG numeric variables will be summarized by treatment group and time with n, mean, SD, SEM, median, Min, and Max values.

The number of available observations and out-of-range values (absolute and in percentage) will be presented. Values outside the investigator's normal range will be flagged in the listing. 'H' and 'L', denoting values above or below the investigator reference range (when present), will flag out-of-range results.

4.4.6 Clinical laboratory tests

All laboratory data (including re-check values if present) will be listed chronologically. 'H' and 'L', denoting values above or below the investigator reference range (when present), will flag out-of-range results. Shift tables will be included for haematology, chemistry and urinalysis.

4.4.6.1 *Haematology and chemistry*

At each time point absolute values and change from baseline of the haematology and chemistry variables will be summarized by treatment group and time with n, mean, SD, SEM, median, Min, and Max values.

4.4.6.2 *Urinalysis*

The categorical data of the urinalysis will be summarized by treatment group and time in frequency tables by variable.

4.4.6.3 Urine Drug screen

Urine drug screen values will be listed.

4.4.6.4 Virology

Virology results values will be listed.

4.4.7 Local tolerability at the injection site (ISR)

The number and percentage of participants with reaction at injection site will be summarized and presented by treatment group and overall.

4.4.8 Participant-reported local tolerability at the injection site and systemic complaints (eDiary app)

All participant-reported reactions at injection site and systemic complaints will be listed and number and percentage of subjects with presence of symptoms and symptom severity, if applicable (refer to code lists in Section 2.2), in each treatment group will be summarized in frequency tables.

4.4.9 Inflammatory markers

At each scheduled visit absolute values and change from baseline of the inflammatory markers will be summarized by using descriptive statistics of n, mean, SD, SEM, median, Min, and Max for each treatment group and overall.

4.5 Analysis of efficacy endpoints

All observed and change from baseline efficacy endpoints will be listed by treatment group, subject and visit. Individual graphs by visit will also be generated.

All observed and change from baseline efficacy endpoints with multiple post-baseline measurements (including but not limited to levels of anti-aSyn, anti-UBITH and anti-CpG1 antibody titers in serum and their antibody parameters of C_{max}, t_{max}, AUC_{last} and $t_{1/2}$, which are derived by non-compartmental analysis and total and free aSyn concentrations in blood) will be summarized using descriptive statistics of n, mean, SD, SEM, median, Min and Max by treatment group, visit (and time when applicable), and will also be presented graphically as mean over time, with standard deviation as error bars.

All observed and change from baseline efficacy endpoints with single post-baseline measurement (including but not limited to levels of anti-aSyn, anti-UBITH and anti-CpG1 antibody titers in CSF and their antibody parameters of C_{max}, t_{max}, AUC_{last} and $t_{1/2}$, which are derived by non-compartmental analysis and total and free aSyn concentrations in CSF, T-cell ELISpot specific for the immunizing peptide as well as MDS-UPDRS Parts II and III sub scores and total scores) will be summarized using descriptive statistics of n, mean, SD, SEM, median, Min and Max by treatment group, and will also be presented graphically as mean in a bar graph, with standard deviation as error bars.

To establish whether significant treatment effects can be detected on the observed efficacy endpoints with multiple post-baseline measurements, such as serum levels of anti-aSyn, anti-UBITH and anti-CpG1 antibody titers in blood, each parameter will be analysed with a mixed model analysis of covariance (ANCOVA) with treatment, time and treatment by time as fixed factors and subject as random factor and the (average) baseline measurement as covariate.

The efficacy endpoints of levels of anti-aSyn, anti-UBITH and anti-CpG1 antibody titers in serum and in CSF will initially be analysed without transformation, but if the data suggest otherwise, log-transformation may be applied. Log-transformed parameters will be back-transformed after analysis where the results may be interpreted as percentage change. Residual Q-Q plots are produced to check the assumption of normality of the error term in the mixed effects models as described above. This is done by visual inspection and the Shapiro-Wilk test statistic.

The observed efficacy endpoints with single post-baseline measurement, such as levels of anti-aSyn, anti-UBITH and anti-CpG1 antibody titers in CSF, will be analysed with a mixed model analysis of variance (ANOVA) with treatment as fixed factors and subject as random factor and the (average) baseline measurement as covariate.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and model parameters will be estimated using the restricted maximum likelihood method.

The general treatment effect and specific contrasts will be reported with the estimated difference and the 95% confidence interval, the least square mean estimates and the p-value. Graphs of the Least Squares Means (LSM) estimates over time by treatment group will be presented with 95% confidence intervals as error bars, as well as change from baseline LSM estimates.

The following contrasts will be calculated within the model using observed data:

- Treatment with 3 vaccinations of 40µg UB-312 versus pooled Placebo
- Treatment with 3 vaccinations of 100 µg UB-312 versus pooled Placebo
- Treatment with 1 vaccination of 40 µg, followed by 2 vaccinations of 300 µg UB-312 versus pooled Placebo
- Treatment with 3 vaccinations of 300 µg UB-312 versus pooled Placebo
- Treatment with 1 vaccination of 40 µg, followed by 2 vaccinations of 1000 µg UB-312 versus pooled Placebo
- Treatment with 3 vaccinations of 1000 µg UB-312 versus pooled Placebo
- Treatment with 3 vaccinations of 2000 µg UB-312 versus pooled Placebo

Notes:

(1) Change from baseline values calculated at subject level for each efficacy endpoint will only be used for descriptive purposes.

(2) Above contrast will be adjusted to obtain for change from baseline endpoints.

(3) The treatment groups across the cohorts will also be compared pairwise.

4.5.1 Inferential methods

The study is exploratory and no formal null hypothesis is set. No adjustments for multiple comparisons will be applied.

4.6 Exploratory analyses and deviations

Exploratory data-driven analyses can be performed with the caveat that any statistical inference will not have any confirmatory value.

Deviations from the original statistical plan will be documented in the clinical study report.

APPENDIX 1 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

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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
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	

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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 **Error! Reference source not found.** of the protocol. Hematology and chemistry results will b e 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.

APPENDIX 2 PROCEDURE & SYNTAX

Analysis	Procedure and Code

AN(C)OVA	For the SAS script:
	▪ period = occasion
	▪ time = expdelta
	▪ subject = subjectnr
	▪ baseline=pre&var
	SAS Proc MIXED Procedure:
	Repeatedly measured:
	`proc mixed data=mix order=internal nobound ;`
	`class subjectnr treatment expdelta occasion ;`
	`model &var=treatment occasion expdelta treatment*expdelta pre&var/ ddfm=KR;`
	`random subjectnr subjectnr*treatment subjectnr*expdelta/type=vc ;`
	`run;`
	
	Single measured:
	`proc mixed data=mix order=internal nobound ;`
	`class subjectnr treatment occasion ;`
	`model &var=treatment occasion pre&var/ ddfm=KR;`
	`random subjectnr/type=vc ;`
	`run;`

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[redacted] [redacted]@vaxxinity.com SVP, Data Science Vaxxinity Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 775AC1C8-E144-45F7-B7EE-30A3840209DC Using IP Address: [redacted] Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/1/2023 1:41:21 PM Viewed: 5/1/2023 4:47:56 PM Signed: 5/1/2023 4:48:43 PM
Electronic Record and Signature Disclosure: Accepted: 7/11/2022 5:53:25 PM ID: 8687599f-392d-476b-b3f9-2e2c5c238178		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
[redacted] [redacted]@vaxxinity.com Security Level: Email, Account Authentication (Required)	COPIED	Sent: 5/1/2023 1:41:21 PM Viewed: 5/1/2023 4:54:29 PM
Electronic Record and Signature Disclosure: Accepted: 4/19/2023 4:02:04 PM ID: a66b2489-3f30-4ceb-9a38-1de34f77c2bb		
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/1/2023 1:41:21 PM
Certified Delivered	Security Checked	5/1/2023 4:47:56 PM
Signing Complete	Security Checked	5/1/2023 4:48:43 PM
Completed	Security Checked	5/1/2023 4:48:43 PM

Payment Events	Status	Timestamps

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