STATISTICAL ANALYSIS PLAN

A Randomized, Double-blind, Placebo-controlled, 3-arm Parallel-group, Multicenter, Phase IIa Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of UBITh® AD Immunotherapeutic Vaccine (UB-311) in Patients with Mild Alzheimer's Disease

Protocol Number: V203-AD	Confidential	Version: v4.0 Final Date: 31Oct2018

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
Aβ	Amyloid β
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
ARIA	Amyloid-Related Imaging Abnormality
ARIA-E	Amyloid-related Imaging Abnormalities: Vasogenic Edema and/or Sulcal Effusion
ARIA-H	Amyloid-related Imaging Abnormalities: Microhemorrhage and Superficial Siderosis
ARWMC	Age-Related White Matter Changes
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urine Nitrogen
BW	Body Weight
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CI	Confidence Interval
CM	Concomitant medicines
CRP	C-reactive Protein
CSR	Clinical Study Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESR	Erythrocyte Sedimentation Rate
HbA1c	Glycosylated Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HIS	Hachinski Ischemic Score
IL	Interleukin
IL-6	Interleukin-6
IL-8	Interleukin-8
IMI	ICON medical imaging
IQR	Interquartile Range
IVRS/IWRS	Interactive Voice/Web Response System
kg	Kilogram
m	Meter

mcg, µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Miligram
mITT	Modified Intention-to-treat
Min	Minimum
Max	Maximum
MMRM	Mixed Model Repeated Measures
mL	Mililiter
mm	Milimeter
MMSE	Mini Mental State Examination
n	Number of Observations Available
NPI	Neuropsychiatric Inventory
PET	Positron Emission Tomography
PP	Per-protocol
PVM	Post-vaccine meningoencephalitis
ROI	Region of Interest
S	Screening
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SUVR	Standard Uptake Value Ratio
TEAE	Treatment-emergent Adverse Event
TNF-α	Tumor necrosis factor-alpha
UNS	United Neuroscience Ltd.
V	Visit
W	Week
WBC	White Blood Cells
WHO	World Health Organization

AMENDMENT HISTORY

Date	Brief description of change
03Jun2016	Update per sponsor's review comments.
02Jul2018	Update per sponsor's review comments.
07Jul2018	Update per sponsor's review comments.
05Sep2018	Update per sponsor's review comments.
12Oct2018	Delete Center from mixed-effects model in section 5.9
29Oct2018	Add the words for "sensitivity analyses" in section 6

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1 INTRODUCTION

This statistical analysis plan (SAP) is consistent with the statistical methods section of the final study protocol (Version 5.0, dated 28Nov 2017) and includes additional detail of efficacy, and safety summaries to be included in the clinical study report (CSR).

Specifically, this document will:

1. Briefly review the objectives, design and endpoints of the study
2. Define the analysis populations
3. Define the rules for determining the outcome of the endpoints
4. Provide an overview of the planned primary and secondary statistical analyses.

The planned analyses identified in this SAP will be included in regulatory submission and/or future manuscripts. Any post-hoc, or unplanned analyses will be clearly identified in the respective CSR. The reader of this SAP is encouraged to also read the clinical protocol for details on conduct of this study, and the operational aspects of clinical assessments and timing for completing a subject in this study.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

The primary objectives of this study are to assess the safety and tolerability of two regimens of UB-311, and to evaluate the immunogenicity of two regimens of UB-311 through measurement of anti-Aβ antibodies.

2.2 Secondary Objectives

The secondary objectives are to evaluate the effects of UB-311 on the changes of cognitive and functional performance over a period of 78 weeks, and to investigate whether UB-311 treatment results in changes in amyloid deposition in vivo by ^{18}F-AV-45 PET imaging.

2.3 Primary Endpoint(s)

The primary endpoints of this study are:

- Safety and tolerability of UB-311 during the study period.
- The immunogenicity of UB-311 as measured by
  - Change from baseline in anti-Aβ antibody levels by the end of study.
  - Response rate.

2.4 Secondary Endpoint(s)

The secondary endpoints are:

- The change from baseline in cognitive, functional, and global assessments by the end of study, including:
  - Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
  - Mini-Mental State Exam (MMSE)
  - Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)

- Clinical Dementia Rating-Sum of Boxes (CDR-SB)
- Neuropsychiatric Inventory (NPI)

- The change from baseline in amyloid deposition by the end of study, including:
  - Mean standard uptake value ratio (SUVR), a composite summary of selected brain regions by the end of study
  - Whole brain amyloid burden (positive or negative) determined by visual assessment

2.5 Exploratory Endpoints

- The change of standard uptake value ratio (SUVR) by region by the end of study.
- AUC of anti-Aβ antibody levels by the end of study.

3 STUDY DESIGN

This is a 78-week, multicenter, randomized, double-blind, placebo-controlled Phase IIa study. Eligible subjects, 60 years or older with mild Alzheimer's disease (AD), will be further screened by ^{18}F-AV-45 PET scan for the presence of amyloid deposition.

Enrolled subjects will be randomized into one of the 3 treatment arms in 1:1:1 ratio. Subjects assigned to Arm 1 will receive 7 doses of UB-311 at Weeks 0, 4, 12, 24, 36, 48, and 60.

Subjects assigned to Arm 2 will receive 5 doses of UB-311 at Weeks 0, 4, 12, 36, and 60, and placebo at Weeks 24 and 48. Subjects assigned to Arm 3 will receive placebo at Weeks 0, 4, 12, 24, 36, 48, and 60. Subjects will be followed until Week 78. Subjects enrolled in the Phase I trial with UB-311 will be excluded from the Phase IIa trial.

4 ANALYSIS VARIABLES

4.1 Demographic 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 summarized by treatment, by study center and overall for the randomized and treated population.

Demographic characteristics are defined as follows:

- Age (in years) to be derived as: (date of informed consent - date of birth)/365.25
- Gender (male/female)
- Body weight (kg)
- Body Mass Index (BMI, kg/m^2): weight in kg/(height in meters)^2
- Race

Disease characteristics including:

- Disease duration (years): (date of informed consent– date of diagnosis)/365.25
- APOE genotype
- Baseline scores of ADAS-Cog total score, MMSE total score, ADCS-ADL total score, CDR/CDR-SB total score, NPI total score

Inflammatory markers including:

- CRP
- ESR
- TNF-α
- IL-6
- IL-8

Physical examination, medical history and concomitant disease, previous and concomitant medication, and HIS score will be described at baseline.

The baseline safety data of clinical chemistry and hematology, inflammatory markers and number of microhemorrhages in the brain will also be summarized.

4.2 Immunogenicity Variables

The level of anti-Aβ antibodies is one of the primary endpoints and is assessed at baseline (V1) and every following visit (V2 to V13). The one-sided 95% confidence interval (CI, right side) from all visits (V1 to V13) for subjects in Arm 3 (placebo group) will be calculated as the threshold of response. Antibody responders will be defined as the subjects with serum antibody titer > response threshold at any visit after baseline.

Response rate, treatment difference and its 90% CI will be calculated.

The AUC of anti-Aβ antibodies will be served as exploratory endpoint. AUC will be calculated by the sum of individual trapezoid area under the curve of level of Aβ antibodies. In case of missing titer values, last observation carry forward will be used for AUC calculation.

4.3 Efficacy Variables

Efficacy variables are evaluated as secondary endpoints in this study.

The change from baseline in cognitive, functional, and global assessments through the end of the study

- Cognition: ADAS-Cog
  - The ADAS-cog 13 contains 13 items, with a total scoring range of 0 – 85 and higher scores indicating greater dysfunction.
- Cognition: MMSE
  - The MMSE is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment and is commonly used in medicine and allied health to screen for dementia. It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time; thus making it an effective way to document a participant's response to treatment. The total score range is 0 – 30 and lower scores indicating greater impairment.
- Function: ADCS-ADL score is range of 0-78 and lower scores indicating greater impairment
- Global: CDR-SB

- The CDR-SB includes six domains (0-3 points/domain), with a total scoring range of 0 – 18 and higher scores indicating greater impartment. The CDR score is calculated at baseline for eligibility check.

- Behavior: NPI:
  - The NPI has 12 domains and for each domain, the relatives assess the frequency of the behaviour (4-point scale), the severity of the symptom (3-point scale) and the emotional stress for the caregiver (6-point scale). The total score of NPI is 0-144 and lower scores indicates greater impairment.

ADAS-Cog, ADCS-ADL, and NPI are rated at baseline (V1), Week 28 (V6), Week 52 (V10) and Week 78 (V13), while MMSE and CDR/CDR-SB are assessed at the first screening (S1), Week 24 (V5), Week 48 (V9) and Week 78 (V13). If a patient withdraws from the study prematurely during the study period or does not have any or some of the scores, the data will be treated as missing values, and no procedure for handling missing assessments will be applied.

4.3.1 SUVR Composite

Mean SUVR change from baseline will be evaluated for a composite target region comprised of a weighted average of selected regions of interests such as frontal, temporal, parietal, occipital and precuneus. The corresponding reference region will be the whole cerebellum for the secondary endpoint. The SUVR is computed as the ratio of the target region signal to the reference region signal.

4.3.2 Semi-Quantitative Visual Assessment

The semi-quantitative visual assessment method will be used to visually assess amyloid burden. The change form baseline in the proportion of PET positive subjects with visual read will be evaluated.

4.3.3 Regional SUVR

Mean SUVR change from baseline will be evaluated for each of the selected brain regions of interest such as frontal, temporal, parietal, occipital and precuneus. The corresponding reference region will be the whole cerebellum. The SUVR is computed as the ratio of the target region signal to the reference region signal.

4.4 Safety Variables

The safety analysis will be based on the reported adverse events and other safety information including:

- Local tolerability at injection site
- Vital signs
- Physical examination
- 12-lead ECG
- Laboratory tests: hematology, clinical chemistry (HbA1c, glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin), and inflammatory parameters (CRP, ESR, TNF-α, IL-6, and IL-8)

- Imaging variables:
    - Amyloid-related imaging abnormality-E (ARIA-E) which includes parenchymal vasogenic edema and/or sulcal (leptomeninges) effusion
    - Amyloid-related imaging abnormality-H (ARIA-H) which includes hemosiderin deposits such as microhemorrhage and superficial siderosis
    - Post-vaccine meningoencephalitis (PVM)
    - Age-related white matter changes (ARWMC)
    - Non-ARIA abnormalities

5 STATISTICAL METHODS

5.1 General

Continuous data will be summarized by treatment group using the number of observations available (n), mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum.

Categorical data will be summarized by treatment group using count and percentage. Missing data will not be categorized in the summaries.

In general, descriptive statistics of quantitative efficacy and safety parameters (results and changes from baseline) by scheduled visit will be provided on observed cases, i.e. the inclusion of only subjects with non-missing assessments at a specific visit.

For undetected value, this study will take the minimum value that can be detected as the text value, eg, <3.5 will be treated as 3.5 and <0.012 will be treated as 0.012 when performing the summary and will list the original value in listing.

- 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.

All statistical tests will be two-sided at the alpha level of 0.05, unless otherwise specified.

5.2 Handling of Dropouts or Missing Data

Partial date of initial diagnosis will be imputed as below:

- If year is missing (or completely missing), do not impute;
- 15th of the month will be used to impute the initial diagnosis date if only the day is missing;
- 01July of the year will be used to impute as the initial diagnosis date if both the day and the month are missing;

ADAS-Cog total score

- The imputed total score of ADAS-Cog-13 when there is only one item is missing due to non- cognitive reasons is presented in:

Missing Question	Imputed Total formula
Word Recall	Observed Total*(1+10/75)
Orientation	Observed total*(1+8/77)
Word Recognition	Observed total*(1+12/73)
Delayed Word Recall	Observed Total*(1+10/75)
All other questions	Observed total*(1+5/80)

- If more than one of 13 items of ADAS-Cog are missing/NA, the total score will be set to missing.

Concomitant Medications Start/End Date

Partial missing start/end date to concomitant medications will be imputed as below:

Start date of concomitant medications

- If only the day of the month is missing, use the first day of the month to replace the missing part.
- If both the day and the month are missing, January 1st will be used to replace the missing part.
- If Day, Month and Year are all missing, use a date one day before the first date of study drug.

End date of concomitant medications

- If only Day is missing, use the last day of the month.
- If Day and Month are both missing, use the last day of the year.
- If Day, Month and Year are all missing, assign 'continuing' status to stop date.

Adverse Event Start/End Date

Missing or partial missing date to the onset date of AE will be imputed as below:

- If the AE onset date is completely missing, the AE start date will be imputed as the first date of study drug;
- If the AE onset date is partial missing, then If both the year and the month are available and the year and the month are the corresponding year and month of the first dosing date, then the AE start date will be imputed as the first dosing date;
    - If both the year and the month are available and the year and the month are not equal to the corresponding year and month of the first dosing date, then the AE start date will be imputed as the 1st date of the month;
    - If only the year is available and the available year is the corresponding year of the first dosing date, then the AE start date will be imputed as the first dosing date;
    - If only the year is available, and the available year is not equal to the corresponding year of the first date of study drug, then the AE start date will be imputed as the January1st of the year;

Adverse event end date will be imputed as below for the partial date only.

- If both the year and the month are available, AE end date will be imputed as the last day

of the month;
- If only the year is available, AE end date will be imputed as the December 31st of the year.
- If the AE onset date is completely missing and status is "ongoing", it will not be imputed

5.3 Analysis Populations

5.3.1 Efficacy populations

The analyses of immunogenicity and efficacy endpoints will be performed by the treatment allocation and based on the modified intention-to-treat and per-protocol populations described below.

Modified intention-to-treat (mITT) population: all randomized subjects 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.

Per-protocol (PP) population: subjects who receive all planned doses of the study drug, complete the treatment period, fulfil all entry criteria, and have no key protocol deviation.

5.3.2 Safety population

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

Safety endpoints and tolerability will be analyzed based on the safety population.

The total number of subjects for each of the following categories will be presented in the clinical study report (CSR).

- Screened subjects: all patients who have signed the inform consent
- Randomized subjects: subjects who receive a randomization number via IVRS/IWRS
- The safety population
- The mITT population
- The PP population

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

- Subjects who have completed the 60-week treatment period
- Subjects who discontinue the study drug during the treatment period

A list of subjects prematurely withdrawn from the study, along with reasons for discontinuation, will be provided.

5.3.3 Subgroups

While this study is not powered for subgroup analyses, select efficacy and safety endpoints will be analyzed by APOE4 carrier subgroups for exploratory purpose.

5.4 Protocol Deviation Reporting

There is a listing for describing the subjects with protocol violation. It will record the details of the

protocol deviation and its severity level.

5.5 Patient Disposition

The number and percentage of screened patients and screened-failure patient will be summarized for all subjects.

The number and percentage of patients who completed the study and who discontinued the study will be summarized by treatment for all subjects. Discontinuations will be further summarized by reason.

The number and percentage of patients in each analysis sets will be summarized by treatment.

5.6 Enrollment by Site

The number and percentage of patients in each study site will be summarized by treatment in mITT, PP and Safety population.

5.7 Subject Demographics and Baseline Characteristics

5.7.1 Subject Demographic Characteristics, Medical History and Diagnoses

The baseline value is defined as the last available value before the first injection of study drug.

Descriptive statistics will be used to summarize the demographic, baseline characteristics data and medical history for the safety population to describe the study population by study center, treatment group and overall.

The distribution of demographic and baseline characteristics among three treatment groups will be evaluated using chi-square or Fisher's exact test for categorical variables and the Kruskal-Wallis test or analysis of variance (ANOVA) for continuous variables.

Pathologies associated with past medical and surgical history will be classified into primary system organ classes and preferred terms using MedDRA 21.0 and will be summarized by study center, treatment group and overall using counts and percentages. The primary system organ classes and preferred terms will be sorted in decreasing order of frequency.

5.7.2 Physical Examination

The number and percentage of abnormality at baseline will be summarized by treatment in Safety population.

Shift from baseline for post treatment at scheduled visit will be summarized by treatment in safety population with number and percentage.

5.7.3 Medical History and Surgery History

Previous/concomitant medical history and surgery history at baseline will be summarized for safety population by treatment with number and percent of patients by primary system organ class and preferred term.

5.7.4 Previous and Concomitant Medications/Therapy

Medications will be classified into the following two groups:

- Previous medications are those that the subject took within 3 months period prior to the first screening visit (S1) and prior to the first administration of the study drug at Week 0

(V1/baseline).
- Concomitant medications are those that the subject 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. Subject will only be counted once within each anatomic and therapeutic class.

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

5.7.5 Baseline Efficacy and Safety Data

For efficacy and safety analysis, the baseline for a given parameter is defined as the last available value prior to the first injection of the study medication. Baseline efficacy and safety variables will be summarized by treatment group, and overall.

5.8 Treatment Tolerability and Compliance

Overall treatment tolerability and compliance will be summarized in safety population.

The overall treatment tolerability of UB-311 for each arm is defined as the percentage of number of administered doses divided by number of administered doses plus number of missed doses of subject(s) who drops out due to drug-related AE(s). It is calculated according to the following formula:

100% x (A+B1+C+D) / (A+B1+B2+C+D)

where

A: number of administered doses of completers

B1: number of administered doses of subject(s) who drops out due to drug-related AE(s)

B2: number of missed doses of subject(s) who drops out due to drug-related AE(s)

C: number of administered doses of subject(s) who drops out due to drug-unrelated AE(s)

D: number of administered doses of subject(s) who drops out not due to AE(s)

The overall compliance is defined as the actual dose (UB-311 or placebo) of injection compared to the prescribed dose of treatment during the study. It is calculated according to the following formula:

100% x (Actual injection dose/Prescribed injection dose)

5.9 Analysis of Immunogenicity Variable

Anti-Aβ antibodies will be summarized by presenting summary statistics of raw data and change from baseline values (n, mean, standard deviation, median, range) at each scheduled visit in mITT Population and PP Population.

The Kruskal-Wallis test or analysis of variance (ANOVA) for continuous variables for baseline information will be performed for comparing the un-adjusted change among Arm 1, Arm 2 and Arm 3.

A repeated-measures mixed-effects model with treatment (Arm 1+ Arm 2 vs. Arm 3, Arm 1 vs. Arm 3 and, Arm 2 vs. Arm 3), study visit, time-by-treatment, APOE4 status, and baseline as a

covariate will be used to analyze change from baseline of anti-Aβ antibodies. The unstructured covariance will be used in the modelling of the within-patient errors in the analysis. For APOE4 status subgroup analysis of MMRM, APOE4 factor will not be considered in the model. AUC of Anti-Aβ antibodies will be used an analysis of covariance (ANCOVA) model with treatment and baseline of Anti-Aβ antibodies as covariate. Antibody responders will be defined as the subjects with serum antibody titer > response threshold at any visit after baseline. The number and percentage of patients will be tabulated for each treatment group in mITT Population and PP Population at each post treatment scheduled visit. Treatment differences in the proportion antibody responders will be analyzed with the Chisq test. The one-sided 95% confidence interval (CI, right side) from all visits (V1 to V13) for subjects in Arm 3 (placebo group) will be calculated as the threshold of response.

5.10 Analysis of Efficacy Data

Efficacy analyses will be performed on the mITT and PP populations. For change from baseline of ADAS-Cog total score, MMSE total score, ADCS-ADL total score, CDR-SB total score, NPI total score, A repeated-measures mixed-effects model with treatment (Arm 1 + Arm 2 vs. Arm 3, Arm 1 vs. Arm 3 and , Arm 2 vs. Arm 3), study visit, time-by-treatment, APOE4 status, and baseline as a covariate will be used to analyze change from baseline. The least square means using maximum likelihood estimate and its 95% will be provided. The unstructured covariance will be used in the modeling of the within-patient errors in the analysis.

For change from baseline of mean SUVR, A repeated- measures mixed-effects model with treatment (Arm 1 + Arm 2 vs. Arm 3, Arm 1 vs. Arm 3 and, Arm 2 vs. Arm 3), study visit, time-by-treatment, APOE4 status, and baseline as a covariate will be used to analyze change from baseline. The unstructured covariance will be used in the modeling of the within-patient errors in the analysis.

For change from baseline of mean SUVR by region, A repeated- measures mixed-effects model with treatment (Arm 1 + Arm 2 vs. Arm 3, Arm 1 vs. Arm 3 and, Arm 2 vs. Arm 3), study visit, time-by-treatment, and baseline as a covariate will be used to analyze change from baseline. The unstructured covariance will be used in the modeling of the within-patient errors in the analysis.

The p-values and confidence intervals for these efficacy endpoints were not adjusted for multiplicity, it should be used for screening purposes only, and that one side of 95% confidence intervals are provided to help gauge the precision of the estimates for treatment difference.

The proportion of PET positive subjects with visual read will be provided by number and percentage for each treatment group in mITT Population and PP Population at each post treatment scheduled visit. Treatment differences will be analysed with the Chisq test. The one-sided 95% confidence interval (CI, right side) between (Arm 1 + Arm 2 vs. Arm 3, Arm 1 vs. Arm 3 and, Arm 2 vs. Arm 3) from all visits will be calculated.

5.11 Subgroup Analysis of Immunogenicity/Efficacy Data

Subgroup analysis by APOE4 carrier will be performed for all immunogenicity and efficacy data, and the analysis model will be the same as the overall analysis.

5.12 Analysis of Safety Data

5.12.1 General

The review of safety and tolerance will be performed on the safety population as defined in Section 5.3.2 Safety Population.

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.

The summary of safety results will be presented by each treatment group.

5.12.2 Adverse Events

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 adverse events

All adverse events are to be coded to a "Preferred Term" and primary "System-organ Class" using the Medical Dictionary for Regulatory Activities (MedDRA).

Summaries of all TEAEs by subjects and events in each treatment group, will include:

- The overview of AEs, summarizing number (n) and percentage (%) 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 (Grades 1 to 5), 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.

Serious adverse events

Serious TEAEs will be summarized and presented as number and percent of subjects and events in each treatment group.

Adverse events leading to treatment discontinuation

TEAEs leading to treatment discontinuation will be summarized and presented as number and percentage of subjects and events in each treatment group.

Local tolerability at injection site

The number and percentage of subjects and events with reaction at injection site will be summarized and presented by treatment group

5.12.3 Clinical Laboratory Assessments

The summaries will include subjects in the safety population with at least one laboratory test

performed during the post-treatment period and, when required by the definition of the abnormality, with an available baseline value and available laboratory normal ranges. For those descriptions, the baseline value will be the last available measure before the first study drug injection.

Descriptive statistics will be used to summarize the laboratory results and the changes from baseline by scheduled visit for each treatment group. Laboratory results will be listed.

5.12.4 Vital Signs

The summaries will include subjects in the safety population who have at least one parameter to be analyzed during the post-treatment period. Descriptive statistics will be used to summarize the results and the changes from baseline value by scheduled visit for each treatment group. The listing will be provided for vital signs data.

5.12.5 12-lead ECG Status

Only ECG status (i.e. normal or abnormal) will be reported. Descriptive statistics will be used to summarize the ECG status and the changes from baseline by scheduled visit for each treatment group. The listing will be provided for ECG data.

5.12.6 Imaging-Related Safety Endpoint

Imaging abnormality events will include the following:

- ARIA-E, ARIA-H,
- ARWMC
- PVM, and
- Non-ARIA abnormalities

All ARIA, PVM, ARWMC and non-ARIA abnormalities will be reported and analyzed as image related abnormalities. ARIA, PVM, ARWMC and non-ARIA abnormalities that appear following first administration of treatment will be reported as imaging related treatment- emergent abnormalities.

An abnormality summary table will be provided for baseline and post-baseline visit by:

- all imaging events including ARIA-E, ARIA-H, Non-ARIA, ARWMC, PVM
- by treatment arm
- by treatment arm and visit

Frequency of ARIA (Presence Yes/No) (Total ARIA, ARIA-E only and ARIA-H only) will be provided with number and percent of patients for baseline visit.

Frequency/Patient of ARIA (Total ARIA, ARIA-E only and ARIA-H only) will be summarized for safety population by treatment with number and percent of patients.

New Events (since last visit) will be summarized for safety population by treatment with number and percent of patients.

Improvement since baseline (ARIA-E and ARIA-H) will be summarized for safety population by treatment with number and percent of patients.

PVM/ARWMC/non-ARIA abnormalities will be summarized for safety population by treatment with number and percent of patients.

The number of ARIA-E/ARIA-H abnormalities will be summarized for safety population by treatment with n, mean, std dev, CV, Q1, median, Q3, Min, Max, L95 and U95.

Distribution of number of ARIA-E/ARIA-H abnormalities by actual value, change from baseline will be summarized for safety population by treatment with number and percent of patients.

Visit value and change from baseline for ARIA-E, ARIA-H and total will be summarized for safety population by treatment with mean and standard deviation.

Overall evaluation of change for ARIA-E/ARIA-H frequency by category (unchanged, improved and worsened) will be summarized for safety population by treatment with number and percent of patients.

Number of occurrences ARIA-E/ARIA-H frequency by brain region (FL, PL, TL, OL, Cer, BS, Oth) will be summarized for safety population by treatment with number and percent of patients by visit.

Overall evaluation of change for ARIA- E/ARIA-H frequency by type will be summarized for safety population by treatment with number and percent of patients.

Overall change from baseline for ARWMC frequency by visit will be summarized for safety population by treatment with number and percent of patients.

Visit value and Change from baseline for ARWMC will be summarized for safety population by treatment with n, mean, std dev, CV, Q1, median, Q3, Min, Max, L95 and U95.

Overall change from baseline for post- vaccine meningoencephalitis frequency by visit will be summarized for safety population by treatment with number and percent of patients.

5.13 Sample Size

This early phase clinical trial is exploratory in nature; hence, the sample size is determined to assess the primary objective of safety, tolerability, and immunogenicity of UB-311. The total of 45 subjects is planned to be enrolled, 15 per arms. For each UB-311-treated arm, 15 subjects are thought to be sufficient to detect an adverse event with an incidence of 7%. Furthermore, 30 subjects receiving UB-311 are anticipated to be able to detect an adverse event with an incidence of 4%.

With the current sample sizes, there may be limited power to detect a reduction in mean SUVRs or regional SUVRs unless there is a dramatic clearance of pre-existing plaques, and extremely limited power to detect effects on cognitive and functional endpoints. These analyses are therefore considered exploratory.

5.14 Interim Analysis

There is no interim analysis for this study.

5.15 Multiplicity

There is only primary immunogenicity endpoint in this study, and all efficacy endpoint will be served as secondary endpoint, and p-Value and its confidence interval will be used for screening purpose, so there is no multiplicity adjustment performed.

5.16 General Conventions for Tables, Listings and Figures

For summary tables, unless otherwise specified, the number of decimal places provided in the SAS output will be based on the accuracy of the least accurate value in the raw data as follows:

- n — integer
- Arithmetic mean — 1 decimal place more than the least accurate number in the raw data
- SD — 2 decimal place more than the least accurate number in the raw data
- CV(%) — 2 decimal places
- Geometric mean — 1 decimal place more than the least accurate number in the raw data
- Median — 1 decimal place more than the least accurate number in the raw data
- Minimum — same number of decimal places as raw data

- Maximum same number of decimal places as raw data
- Confidence interval same number of decimals as the associated statistic
- Geometric mean ratio 2 decimal places

6 CHANGES FROM THE PROTOCOL TO THIS SAP

Additional details and specifications have been included in this SAP to allow for better understanding of the intended methods. Additional analyses (including exploratory and subgroup assessments) for select variables have been added. Additional sensitivity analyses will be conducted to explore any effects related to the presence of data outliers.