UNITED NEUROSCIENCE

CLINICAL TRIAL PROTOCOL

Investigational Product:
UBITh® AD Immunotherapeutic Vaccine (UB-311)

An Extension Study of a Phase IIa study in Patients with Mild Alzheimer's Disease to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of UBITh® AD Immunotherapeutic Vaccine (UB-311)

Protocol Number: V203-AD-EXT	***Confidential***	Version: 1.1 Date: 22-Jan-2018

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Principal Investigator's Signature Page

I understood the obligations as a clinical trial investigator and agree to perform and report the study in compliance to the protocol, good clinical practice (GCP), and the current rules and regulations set forth by the applicable health authorities.

Name	Affiliation	Signature	Date

Co-Investigator's Signature Page

I understood the obligations as a clinical trial investigator and agree to perform and report the study in compliance to the protocol, good clinical practice (GCP), and the current rules and regulations set forth by the applicable health authorities.

Name	Affiliation	Signature	Date

Internal Signature Page

I understood the obligations as an officer providing service in the organization(s) listed on the cover page of this document, and agreed to perform the study in my responsible aspects, in compliance to the protocol and good clinical practice (GCP) and the current rules and regulations set forth by the applicable health authorities.

Affiliation	Name	Position	Signature	Date
United Neuroscience Ltd., Taiwan				

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABBREVIATION	TERM
Aβ	Amyloid β
AChE	Acetyl Cholinesterase
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
ARIA	Amyloid-related Imaging Abnormalities
ARIA-E	Amyloid-related Imaging Abnormalities: Vasogenic Edema and/or Sulcal Effusion
ARIA-H	Amyloid-related Imaging Abnormalities: Microhemorrhage and Superficial Siderosis
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urine Nitrogen
BW	Body Weight
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CI	Confidence Interval
CNS	Central Nerves System
CpG-ODN	Cytosine-phosphate-guanosine Oligodeoxynucleotide
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAD	Disability Assessment for Dementia
dL	Deciliter
DNA	Deoxyribonucleic Acid
DOH	Department of Health
ECG	Electrocardiogram
EDTA	Ethylenediamine Tetra Acetic Acid
EIA	Enzyme Immunoassay
ELISPOT	Enzyme-Linked ImmunoSpot
ESR	Erythrocyte Sedimentation Rate
ET	Early Termination

GCP	Good Clinical Practice
GFAP	Glial fibrillary acidic protein
HbA1c	Glycosylated Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
IL-6	Interleukin-6
IL-8	Interleukin-8
IM	Intramuscular
IQR	Interquartile Range
IRB	Institutional Review Board
IU	International Unit
kg	Kilogram
KS-CGMH	Kaohsiung Chang Gung Memorial Hospital
LK-CGMH	Linkou Chang Gung Memorial Hospital
m	Meter
MCI	Mild Cognitive Impairment
mcg, µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intention-to-treat
mL	Milliliter
mm	Millimeter
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
n	Number of Observations Available
NCI	National Cancer Institute
NFH	Neurofilament Heavy Chain
NFL	Neurofilament Light Chain
NMDA	N-methyl-D-aspartate
NTB	Neuropsychological Test Battery
NTUH	National Taiwan University Hospital
PE	Physical Examination
PET	Positron Emission Tomography
PP	Per-protocol
PSD	Power spectral densities

ROI	Region of Interest
S	Screening
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SSRIs	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUVR	Standard Uptake Value Ratio
TEAE	Treatment-emergent Adverse Event
TNF-α	Tumor necrosis factor-alpha
TVGH	Taipei Veterans General Hospital
UCHL1	Ubiquitin C-Terminal Hydrolase L1
UNS	United Neuroscience Ltd.
ULN	Upper limits of normal
ULRR	Upper Limit of Reference Range
US FDA	United States, Food and Drug Administration
V	Visit
W	Week
WBC	White Blood Cells
WHO	World Health Organization

SYNOPSIS

PROTOCOL NUMBER	V203-AD-EXT
TITLE	An Extension Study of a Phase IIa study in Patients with Mild Alzheimer's Disease to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of UBITh® AD Immunotherapeutic Vaccine (UB-311)
STUDY SITES	There will be four study sites: Site 1: Taipei Veterans General Hospital (TVGH) Principal Investigator: Dr. Pei-Ning Wang Site 2: National Taiwan University Hospital (NTUH) Principal Investigator: Dr. Ming-Jang Chiu Site 3: Linkou Chang Gung Memorial Hospital (LK-CGMH) Principal Investigator: Dr. Chin-Chang Huang Site 4: Kaohsiung Chang Gung Memorial Hospital (KS-CGMH) Principal Investigator: Dr. Chiung-Chih Chang
STUDY OBJECTIVES	To assess the long-term treatment effects of UB-311 on: 1. Safety and tolerability of UB-311; 2. Immunogenicity of UB-311; 3. Change in cognitive and functional performance; 4. Change in qEEG; 5. Change of brain volume and cortical thickness 6. Change in amyloid deposition evaluated by ^{18}F-AV-45 PET imaging; 7. Change in neurodegenerative biomarkers; 8. Correlation between the titers of anti-Aβ antibody and anti-measles or anti-HBV cellular and humoral immune memory
STUDY DESIGN	This is a 108-week extension study in patients with mild Alzheimer's disease (AD) who participated in V203-AD trial, a multicenter, randomized, double-blind, placebo-controlled phase IIa study of UB-311. Subjects from UB-311 treatment groups (Arm 1 with a 3-month treatment interval and Arm 2 with a 6-month treatment interval) in V203-AD study will receive total 3 doses of UB-311 at weeks 1, 49 and 97 and 2 doses of placebo at weeks 5 and 13 as treatment group 1. Subjects from placebo treatment group (Arm 3) in V203-AD study will receive total 5 doses of UB-311 at weeks 1, 5, 13, 49 and 97 as treatment group 2. Subjects will be followed till Week 109. To maintain the blinding of V203-AD study, the first three

	injections at weeks 1, 5 and 13 in this extension study will keep blinded before the end of V203-AD study.
STUDY POPULATION **Total expected number of subjects**	Subjects from V203-AD trial (maximum 42 subjects) will be eligible to join this extension study.
Inclusion criteria	Subjects may be included in the clinical trial only if they meet **all** of the following criteria: 1. Patients who participated in V203-AD trial without major safety concerns; 2. The last UB-311/placebo injection received in V203-AD study should be at least 24 weeks prior to the V1 of this extension study; 3. Stable doses of permitted medications for 3 months before screening, such as acetyl cholinesterase (AChE) inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonist, ergot alkaloids or their derivatives for cognitive enhancement; 4. Female must either be post-menopausal (no menstrual period for >1 year), surgically sterilized or agree to avoid becoming pregnant during the entire period of this study; while sexually active fertile male must agree to use effective birth control methods throughout the study duration, if their sexual partner(s) are women of childbearing potential; 5. With a caregiver who has frequent contact with the subject (e.g. an average of 10 hours per week or more) and agrees to sign the informed consent form (ICF) and to perform study-related AD scales; 6. Both patient and his/her caregiver should sign the written informed consent before undergoing any study procedures; and 7. Agree not to donate blood or blood products for transfusion during the study and for 3 months thereafter
Exclusion criteria	Subjects will be excluded from the clinical trial for **any** of the following reasons: 1. Clinically significant neurological disease other than Alzheimer's disease, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities;

	2. Screening magnetic resonance imaging (MRI) scan with evidence of central nerves system (CNS) infection, infarction, or other focal lesions, cerebrovascular disease, superficial siderosis, macrohemorrhage, microhemorrhages, multiple lacunes or lacunes in a critical memory structure accompanies with symptoms that the investigator determines to be a safety concern; 3. Major depressive episode or manic episode as described in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) within the past 1 year before screening. Psychotic features, agitation or behavioural problems within the last 3 months before screening which could lead to difficulty in complying with the protocol; 4. History of schizophrenia (DSM-V criteria); 5. Any significant systemic illness or unstable medical condition which could lead to difficulty in complying with the protocol; 6. History of alcohol or substance abuse or dependence within the past 2 years before screening (DSM-V criteria); 7. History of autoimmune disease, including but not limited to ankylosing spondylitis, Sjogren's syndrome, systemic lupus erythematosus, rheumatic arthritis, or multiple sclerosis; 8. History of severe systemic disease that may affect a subject's participation at the investigator's discretion; 9. History of anaphylaxis; other serious adverse reactions to any vaccine; or any serious allergic reactions to medications requiring treatment; 10. Use of any prohibited medications within 4 weeks prior to screening; 11. Use of any investigational drug within 4 weeks before screening; 12. Previous exposure to any anti-Aβ immunotherapy except UB-311; 13. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved); 14. Received blood or blood derivatives treatment within 3 months prior to screening; 15. Current or recent participation (within 12 months before screening) in any procedures involving radioactive agents such that radiation exposure of the subject in any given year would exceed the whole-body limits of annual and total dose

	commitment of 5 rems set forth in the US Code of Federal Regulations (CFR) Title 21 section 361.1; 16. Abnormal clinical laboratory values judged by the investigator to be a safety concern to join the study
INVESTIGATIONAL PRODUCT(S)	The UB-311 (UBITh® AD Immunotherapeutic Vaccine) is supplied as a single-dose vial containing 300 μg in 0.5 mL solution.
PRIMARY ENDPOINT(S) AND MAIN SECONDARY ENDPOINT(S)	**Primary endpoints:** • Safety and tolerability: the incidence of adverse event (AE)/serious adverse event (SAE); and • The immunogenicity of UB-311 as measured by change in anti-Aβ antibody levels and response rate. **Secondary endpoints:** The treatment effects of UB-311 on: • The change in cognitive and global assessments, including: – Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) – Mini-Mental State Exam (MMSE) – Clinical Dementia Rating-Sum of Boxes (CDR-SB) – Computerized cognitive tests • The change from baseline of V203-AD study in amyloid deposition by ^{18}F-AV-45 PET imaging; **Exploratory endpoints:** • Titers of anti-$A\beta_{1-42}$ monomer and anti-$A\beta_{1-42}$ oligomer antibodies; • The change in qEEG; • The change of brain volume and cortical thickness; • The change in neurodegenerative biomarkers in blood such as $A\beta_{40}$, $A\beta_{42}$, tau, neurofilament heavy chain (NFH), neurofilament light chain (NFL), glial fibrillary acidic protein (GFAP) and ubiquitin C-Terminal Hydrolase L1 (UCHL1); • The correlation between titers of anti-Aβ antibody with anti-measles or anti-HBV antibodies and memory T cell responses for UBITh® 1 and UBITh® 2.
STATISTICAL CONSIDERATIONS	The overall treatment tolerability of UB-311 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: $100\% \times (A+B_1+C+D)/ (A+B_1+B_2+C+D)$

	where A: number of administered doses of completers B_1: number of administered doses of subject(s) who drops out due to drug-related AE(s) B_2: 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) **Analysis Population** Modified intent-to-treat (mITT) population: all 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. Safety population: subjects exposed to at least one dose of the study drug. The analyses of primary safety variables and tolerability will be performed on safety population, and the analyses of immunogenicity and efficacy endpoints will be performed on both mITT and PP populations. For the analyses of immunogenicity, UB-311 response rate will be calculated and the change in antibody level will also be compared by a repeated-measures mixed-effects model. For the analyses of efficacy, continuous variables with repeated measures will be analyzed using a mixed-effects model.
DURATION OF STUDY PERIOD	Screening period: ≤6 weeks Treatment period: 96 weeks Follow-up period: 12 weeks

1. INTRODUCTION AND RATIONALE

Alzheimer's disease (AD), a progressive, multifactorial, and heterogeneous neurodegenerative disease, affects 47 million people worldwide and the number is projected to increase to more than 131 million by 2050[1]. Several early community-based studies have shown that AD is the most common cause of dementia in Taiwan with prevalence ranging from 1.7 to 4.4%[2-4] and an incidence rate of about 0.817%[5] in 2010.

Alzheimer's disease is characterized by extracellular aggregates of amyloid β (Aβ) protein and intracellular tangles of the neurofilament protein tau, both are toxic to neurons. Therefore, Aβ has been a major therapeutic target in Aβ immunotherapy. Although symptomatic therapies are available, there is still no proven treatment that can address a variety of neurobehavioral disturbances and reverse progression of AD[6-7]. It has been shown that reducing Aβ deposition is able to improve cognition function in animal models of AD. Recently released human clinical trial results of Aducanumab, a human monoclonal antibody targeting aggregated forms of β-amyloid developed by Biogen Inc[8] also supports this notion. Unlike this passive immunity approach, the goal for an active Aβ immunotherapy is to stimulate an immune response to generate robust endogenous anti-Aβ antibodies that ultimately reduce brain Aβ levels. UBITh® AD active immunotherapeutic vaccine (UB-311) is comprised of two $Aβ_{1-14}$-targeting peptide immunogens (B-cell epitopes) each linked to proprietary, synthetic helper T-cell peptide epitopes (UBITh®) formulated in a Th2-biased delivery system designed to minimize T-cell inflammatory reactivity[9-12]. Studies in small animals, baboons and macaques showed that anti-Aβ antibodies were generated with the expected N-terminus site-specificity by UB-311.

The neurodegenerative processes in AD lead to the loss of synapses and dysfunction of brain electrical circuits. Quantitative electroencephalograhy (qEEG) is a clinical tool commonly used to non-invasively assess brain synaptic and circuit function. Studies have shown abnormal frequency power spectra and functional connectivity of resting state electroencephalographic (EEG) rhythms in subjects with AD compared to healthy age-matched elderly subjects. Alzheimer's patients are typically characterized by a slowing of EEG, including an increase in delta and theta power and a decrease in alpha and beta[13-15]. EEG is thus a noninvasive, low cost and widely available biomarker to identify dementia and classify the degree of its severity by signal processing and analysis. qEEG will be used to track brain neurophysiology changes in this study.

In addition to the imaging biomarker, ^{18}F-AV-45 PET, peripheral blood based biomarker assays will also be performed throughout the study for AD progression and UB-311 therapeutic effect. These include $Aβ_{40}$, $Aβ_{42}$, Tau, Neurofilament heavy chain (NFH), Neurofilament light chain (NFL), glial fibrillary acidic protein (GFAP), and ubiquitin C-terminal Hydrolase L1 (UCHL1).

In the phase I study (V118-AD) of UB-311, all 19 subjects completed the study and only 16 mild or moderate treatment-related AE episodes were reported in 9 subjects. Injection site reaction was the most frequently reported AE[16]. An UB-311 Phase IIa study (V203-AD) with an identical 3-arm, randomized, double-blind, placebo-controlled trial design is underway in Taiwan and 43 patients has been enrolled. In V203-AD study, subjects receive 7 doses of UB-311, 5 doses of UB-311 and 2 doses of placebo or 7 doses of placebo utilizing 1:1:1 randomization scheme. Until Oct 2017, 25 patients have completed the treatment period containing 7 injections of study drug and all patients have received 4 injections of study drug. To evaluate the long-term safety, tolerability and potential efficacy, patients who previously participated in V203-AD study will be eligible to participate in

the extension study and will receive 3 or 5 doses of UB-311 within a 96-week treatment period followed by a 12-week follow-up period. Assessments such as cognitive and global performance, amyloid PET imaging, EEG, brain volume/cortical thickness and fluid neurodegenerative biomarkers will be performed to evaluate the AD progression and treatment effect.

2 OBJECTIVES

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

The secondary objectives are to evaluate the effects of UB-311 on the changes of cognitive and global performance and to investigate whether UB-311 treatment results in group differences and changes in amyloid deposition *in vivo* evaluated by ^{18}F-AV-45 PET imaging. In addition, the change of qEEG, brain volume/cortical thickness and level of neurodegenerative biomarkers in blood will be assessed for AD progression and UB-311 efficacy evaluation.

UBITh®1 and UBITh®2 epitopes are idealized T helper (Th) cell designs based on and modified from Th sites on measles virus F protein and hepatitis B surface antigen, respectively. To evaluate if subjects who previously infected with measles/HBV or immunized with measles/HBV vaccines will generated higher titer of anti-Aβ antibody by UB-311, titers of anti-measles and anti-HBV antibodies will be compared to the maximum titer of anti-Aβ antibody in subjects. In addition, an evaluation for T-cell memory status against UBITh® 1 and UBITh® 2 will also be performed in peripheral blood isolated monocytic cells.

3 TRIAL DESIGN

This is a 108-week extension study of V203-AD multicenter Phase IIa trial.

Individuals who participated in V203-AD trial will be eligible to join the extension study.

3.1 Description of the Protocol

The study comprises 3 periods as shown in Table 3.1 (please also see 8.2 Events and Time Schedule):

- An up to 6-week screening period to complete screening visit,
- A 96-week treatment period, and
- A 12-week follow-up period.

Table 3.1 Clinical Schematic Diagram

	Screening	Treatment							Follow-up
Visit	S1	V1	V2	V3	V4	V5	V6	V7	V8
Week	-6 ~ -1	1	5	13	25	49	73	97	109
Treatments									
1. For UB-311 treatment groups (arm 1 and 2) from V203-AD		↑	↑P	↑P		↑		↑	
2. For placebo group (arm 3) from V203-AD		↑	↑	↑		↑		↑	

↑: UB-311 ↑P: placebo

3.1.1 Screening Period

Subjects who completed the last injection in V203-AD study at least 24 weeks prior to the V1 of this extension study are screened within the screening period (Weeks -6~-1). All tests required for evaluating the eligibility of the subjects are performed at S1. If a subject's last MRI scan in V203-AD study is within 3 months before the screening visit of this extension study, an MRI is not required for screening. The data of last MRI scan from V203-AD can be used for eligibility/safety evaluation in the extension study

3.1.2 Treatment Period

Subjects meeting all inclusion criteria and presenting no exclusion criteria enter the treatment period, from V1 (Week 1) to V7 (Week 97).

Because the purpose of giving placebo in this extension study is to maintain the blindness of V203-AD study, placebo will not be given to subjects after unblinding of V203-AD study.

3.1.3 Follow-up Period

The follow-up period comprises 1 visit: V8 (Week 109)

3.2 Endpoints

3.2.1 Primary

The primary endpoints of this study are:

- Safety and tolerability of UB-311: incidence of adverse event (AE)/serious adverse event (SAE).
- The immunogenicity of UB-311 as measured by
  - Change in anti-Aβ antibody levels
  - Response rate (see section 6.1.2 for definition)

3.2.2 Secondary

The secondary endpoints are to measure the treatment effects of UB-311 on:

- The change in cognitive and global assessments, including:
  - Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
  - Mini-Mental State Exam (MMSE)
  - Clinical Dementia Rating-Sum of Boxes (CDR-SB)
  - Computerized cognitive tests
- The change from baseline of V203-AD study in amyloid deposition by ^{18}F-AV-45 PET imaging;

2.2.3 Exploratory

- Titers of anti-Aβ_{1-42} monomer and anti-Aβ_{1-42} oligomer antibodies;
- The change in qEEG;
- The change of brain volume and cortical thickness;
- The change in neurodegenerative biomarkers such as Aβ_{40}, Aβ_{42}, tau, NFH, NFL, GFAP and UCHL1; and
- The correlation between titers of anti-Aβ antibody and anti-measles or anti-HBV antibodies as well as memory T cell response for UBITh® 1 and UBITh® 2.

The changes in anti-Aβ antibody levels, cognitive and global assessments, PET, qEEG, brain volume and cortical thickness and neurodegenerative biomarkers in blood will be compared between the 3 treatment groups from V203-AD study. If subjects agree to provide his/her remaining specimens from V203-AD for neurodegenerative biomarkers analysis, the data will be also compared from baseline in V203-AD study between 3 treatment groups.

3.3 Description of Blinding Methods

The UB-311 and placebo vials are indistinguishable by appearance. Knowing which study drug (UB-311 or placebo) is given in the second and third injections of the extension study will jeopardize the blindness of the V203-AD study, so we will reserve the blindness of the first three injections until the end of ongoing V203-AD study. Investigators do not have access to the information of randomization code and treatment arm of each subject until the V203-AD study is completed except under circumstances described in section 6.4. To maintain the blindness of V203-AD study, neither the investigator nor the sponsor will have access to the data that could potentially compromise study blindness before the end of V203-AD study.

3.4 Stopping Rules

The scientific measures of treatment that correspond to early termination are safety.

In the event of an unexpected and suspected SAE that results in a life-threatening condition or death, the principal investigator(s) will assess the relationship between SAE and the study drug according to the subject's clinical symptoms, clinical data, characteristics of the study medicine and safety

endpoints, such as MRI results. If the causality assessment confirms that the SAE is definitely related to the study drug, and the Institutional Review Board (IRB) and Department of Health (DOH) express consensus opinions, the clinical trial might be stopped. The subject will receive immediate clinical treatment for the adverse event and will not receive additional administrations of the study medicine.

After this trial ends, all attempts should be made to follow up all subjects through telephone calls or by direct contact, in order to document any delayed or unresolved adverse drug reactions or adverse events.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Number of Subjects

Subjects from V203-AD trial (maximum 42 subjects) will be eligible to join this extension study.

4.2 Inclusion Criteria

For inclusion in the study subjects must fulfil all of the following criteria:

1. Patients who participated in V203-AD trial without major safety concerns;
2. The last UB-311/placebo injection received in V203-AD study should be at least 24 weeks prior to the V1 of this extension study;
3. Stable doses of permitted medications for 3 months before screening, such as acetyl cholinesterase (AChE) inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonist, ergot alkaloids or their derivatives for cognitive enhancement;
4. Female must either be post-menopausal (no menstrual period for >1 year), surgically sterilized or agree to avoid becoming pregnant during the entire period of this study; while sexually active fertile male must agree to use effective birth control methods throughout the study duration, if their sexual partner(s) are women of childbearing potential;
5. With a caregiver who has frequent contact with the subject (e.g. an average of 10 hours per week or more) and agrees to sign the informed consent form (ICF) and to perform study-related AD scales;
6. Both patient and his/her caregiver should sign the written informed consent before undergoing any study procedures; and
7. Agree not to donate blood or blood products for transfusion during the study and for 3 months thereafter.

4.3 Exclusion Criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Clinically significant neurological disease other than Alzheimer's disease, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities;
2. Screening magnetic resonance imaging (MRI) scan with evidence of central nerves system (CNS) infection, infarction, or other focal lesions, cerebrovascular disease, superficial siderosis, macrohemorrhage, microhemorrhages, multiple lacunes or lacunes in a critical memory structure accompanies with symptoms that the investigator determines to be a safety concern;
3. Major depressive episode or manic episode as described in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) within the past 1 year before screening. Psychotic

features, agitation or behavioural problems within the last 3 months before screening which could lead to difficulty in complying with the protocol;

4. History of schizophrenia (DSM-V criteria);
5. Any significant systemic illness or unstable medical condition which could lead to difficulty in complying with the protocol;
6. History of alcohol or substance abuse or dependence within the past 2 years before screening (DSM-V criteria);
7. History of autoimmune disease, including but not limited to ankylosing spondylitis, Sjogren's syndrome, systemic lupus erythematosus, rheumatic arthritis, or multiple sclerosis;
8. History of severe systemic disease that may affect a subject's participation at the investigator's discretion;
9. History of anaphylaxis; other serious adverse reactions to any vaccine; or any serious allergic reactions to medications requiring treatment;
10. Use of any prohibited medications within 4 weeks prior to screening;
11. Use of any investigational drug within 4 weeks before screening;
12. Previous exposure to any anti-Aβ immunotherapy except UB-311;
13. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved);
14. Received blood or blood derivatives treatment within 3 months prior to screening; and
15. Current or recent participation (within 12 months before screening) in any procedures involving radioactive agents such that radiation exposure of the subject in any given year would exceed the whole-body limits of annual and total dose commitment of 5 rems set forth in the US Code of Federal Regulations (CFR) Title 21 section 361.1.
16. Abnormal clinical laboratory values judged by the investigator to be a safety concern to join the study

4.4 Subject Withdrawal Criteria

A subject may withdraw from the study treatment or the study due to the following reasons:

1. Lost to follow up.
2. The subject withdraws consent.
3. Development of an imaging abnormality consistent with vasogenic edema, macrohemorrhage, or an area of superficial siderosis appears or a clinically symptomatic microhemorrhage.
4. Development of intolerable adverse event due to study treatment as determined by the investigator and/or subject.
5. Development of an intercurrent illness or condition for which the subject requires concomitant medications which are not allowed in the study.
6. Discovery that the subject entered the study in violation of the protocol or occurrence of a protocol violation during the study that may affect safety at the investigator's discretion.

7. Subject's pregnancy.
8. Subject's death.
9. The investigator feels that in the best interest of the subject's health, the subject is to be withdrawn from the trial.
10. Data not known before starting the trial become available and raise concern about the safety of the study drug such that continuation would pose potential risk to any particular subject.

The type and timing of the data to be collected and follow-up for withdrawn subjects

When a subject decides to withdraw from the study treatment or the study, he/she should be contacted to obtain information about the reason(s) for discontinuation and any adverse events. For subjects who withdraw from the study treatment or the study after study drug administration, efforts will be made, as appropriate and at discretion of investigator, to have an early termination (ET) visit arranged as soon as possible. All study procedures listed in Visit 8/ET (see sections 8.2) should be completed at the early termination visit when applicable. In addition, subjects will be encouraged to complete all remaining scheduled visits and procedures before the early termination visit.

If a subject is withdrawn at a scheduled study visit, the early termination visit could be conducted on the same day. Besides, in the event of a drop-out after study drug administration, all attempts should be made to follow-up the subject through telephone calls or by direct contact until the end of this study (Week 109) in order to document any delayed adverse drug reactions or adverse events.

5 TREATMENT OF SUBJECTS

5.1 Description of Study Drug

Study drug: UB-311 (UBITh® AD Immunotherapeutic Vaccine), 300 µg per 0.5 mL per vial.

5.2 Dosing Regimens and Rationale

Eligible subjects will receive total 3 or 5 doses of UB-311 depends on which treatment arm they were in V203-AD study. Subjects from placebo treatment group (Arm 3) in V203-AD study will receive total 5 doses of UB-311 at weeks 1, 5, 13, 49 and 97. Subjects from UB-311 treatment groups (Arm 1 and 2) in V203-AD study will receive total 3 doses of UB-311 at weeks 1, 49 and 97 and 2 doses of placebo at weeks 5 and 13. Placebo will not be given to subjects after unblinding of V203-AD study.

The long-term safety, tolerability and efficacy of UB-311 will be evaluated during the extension study. Considering the requirement of priming doses to elicit comparable anti-Aβ antibody titer, subjects from placebo treatment group (Arm 3) in V203-AD study will receive UB-311 at Weeks 5 and 13 and UB-311 treatment groups (Arm 1 and 2) from V203-AD study will receive placebo at Weeks 5 and 13 to avoid unblinding of V203-AD study.

UB-311/placebo will be given via intramuscular (IM) injection on alternate arms or at different sites, which will be recorded.

5.3 Handling of Study Drug

5.3.1 Packing and Labelling

The drug is suitably packaged to protect it from alteration, contamination, and damage during storage, handling, and shipping. The treatment boxes containing UB-311/placebo are labelled with subject's number, storage condition, and manufacturer and the vials are placed in the order of injection. The blindness of the first three injections will be reserved until the end of ongoing V203-AD study.

5.3.2 Storage

The study drugs have to be stored between 2°C and 8°C. The study drugs at each study site must be properly stored, under the responsibility of the investigator or the pharmacist in accordance with the storage conditions indicated on the label. The monitor should check the storage conditions during the monitoring visits.

5.4 Drug Accountability

The study drugs should be kept in pharmacy of each study site, and be administered to subjects in the clinical trial under the responsibility of the investigator. In addition, the investigator should keep accurate drug delivery records. Any study drug accidentally or deliberately destroyed should be accounted for and documented. Any discrepancies between the amounts dispensed and those returned should be explained.

After the end of the study, all used and unused vials of study drug should be packed, sealed, and returned to UNS. All remaining study drugs should be destroyed by UNS or its designee.

5.5 Concomitant Medicines

All concomitant medications should be recorded in the case report form (CRF).

5.5.1 Permitted Medicines

Permitted medicines/treatments are subject's routinely used medications or the treatments which are judged by the investigator as not to affect the efficacy and safety assessments in the study.

In addition, the following medications may be permitted:

- Acetyl cholinesterase inhibitors (donepezil hydrochloride, rivastigmine tartrate, tacrine, galantamine); N-methyl-D-aspartate (NMDA) receptor antagonist (memantine); ergot alkaloids and their derivatives, must be on stable dose for at least 3 months prior to the screening visit. During the study period, subjects may adjust the dose of permitted medicines if determined to be needed by the investigators.
- Ginkgo biloba
- Piracetam (Nootropil)
- Vitamin E (≤400 IU/day)

5.5.2 Prohibited Medicines

The following medications are prohibited within 4 weeks prior to the screening visit and during the study period:

- Antiparkinson's drugs (e.g. L-dopa, dopamine agonists, amantadine)
- Neuroleptics, with the exception of haloperidol ≤2 mg/day, quetiapine ≤300 mg/day, risperidone ≤2 mg/day, sulpiride ≤200 mg/day, and olanzapine ≤10 mg/day
- Sedative/hypnotics (in exceptional cases where short-acting and intermediate-acting benzodiazepines are conditionally allowed, for example, midazolam in oral dosage ≤7.5 mg/day for sleep only, midazolam injection ≤5 mg/day for office procedures with sedation only, oxazolam ≤10 mg/day, alprazolam ≤1 mg/day, lorazepam ≤1 mg/day, bromazepam ≤12 mg/day with maximum starting dose of 1.5 mg, twice a day, estazolam ≤1 mg/day at bedtime for sleep only, and other hypnotics such as zolpidem ≤10 mg/day, and zopiclone ≤7.5 mg/day may be allowed during the study
- Antidepressants (e.g. bupropion, imipramine, mirtazapine, nefazodone and trazodone) with the exception of selective serotonin reuptake inhibitors (SSRIs), e.g. fluoxetine, paroxetine, sertraline, fluvoxamine, escitalopram, citalopram and serotonin-norepinephrine reuptake inhibitors (SNRIs), e.g. venlafaxine, duloxetine, milnacipran, desvenlafaxine
- Heparin or thrombolytic therapy starting from 4-week screening period

- Other treatments, including traditional herbal medicines and nutritional supplements, that may disturb the study result at investigator's discretion

5.6 Subject Compliance

The compliance to the study treatments will be checked by the investigator and study drug administration will be recorded in the CRF.

6 ASSESSMENT OF INVESTIGATIONAL PRODUCT

6.1 Immunogenicity

Immunogenicity is evaluated as one of the primary endpoints in this study.

- Change in anti-Aβ antibody levels till the end of the study (Week 109)
- Response rate (see section 6.1.2 for definition)

6.1.1 Anti-Aβ antibody measurement

For the immunogenicity assessment of the investigational product, UB-311, the level of anti-Aβ antibodies in the serum samples will be measured by a validated enzyme immunoassay manufactured by United Biomedical, Inc. (UBI).

The level of anti-Aβ antibodies is assessed at every visit throughout the study period from V1 to V8 except V4 and V6 (Weeks 1, 5, 13, 49, 97 and 109). For visits that UB-311/placebo is scheduled to be administrated (V1, V2, V3, V5 and V7), blood samples will be collected before the treatment.

6.1.2 Response rate

Antibody responder is defined as the study subject whose serum antibody titer is greater than the response threshold (see section 9.1.2 for definition) at any visit after V1. Response rate will be calculated as the percent of the number of antibody responders versus the total number of subjects.

6.2 Safety

The study-specific and general safety criteria are described in section 7.1 (Safety Endpoints).

A patient card, including the relevant “24 hour alert system” telephone number, will be provided to every subject who participates in the study.

6.3 Efficacy

Efficacy variables are evaluated as secondary and exploratory endpoints in this study.

6.3.1 Evaluation variables

6.3.1.1 The change in cognitive and global assessments till the end of the study (Week 109)

- Cognition: ADAS-Cog, MMSE and computerized cognitive test
- Global: CDR-SB

6.3.1.2 The change of amyloid burden in retention of ^{18}F-AV-45

The data will be expressed by mean regional standard uptake value ratio (SUVR) in the selected regions of interests (ROIs). The baseline of V203-AD study will be used to assess the change of

amyloid deposition during the study.

6.3.1.3 The change in qEEG over the period extension study

The absolute and relative power spectral densities (PSDs) will be calculated for each 1 second epoch (1-40 Hz bins), and also grouped into the standard EEG bandwidths: delta, theta, alpha, sigma, beta, and gamma. Additionally, the PSD variables will be averaged across brain regions of interest, including: frontal, central, parietal, anterior, temporal, and left/right brain regions. Global power in each band will be calculated by averaging power values for all channels.

6.3.1.4 The change of brain volume and cortical thickness

Alzheimer's disease leads to nerve cell death and tissue loss throughout the brain. Over time, the brain shrinks dramatically, affecting nearly all its functions. Therefore, the change of brain volume and cortical thickness will be evaluated via MRI scans.

6.3.1.5 The change in neurodegenerative biomarkers over the period of extension study

The concentration of neurodegenerative biomarkers such as $A\beta_{40}$, $A\beta_{42}$, tau, NFH, NFL, GFAP and UCHL1 will be measured and compared during the study to evaluate their correlation with disease progression and treatment efficacy of UB-311.

6.3.1.6 The correlation between titers of anti-Aβ antibody and anti-measles or anti-HBV antibodies as well as memory T cell response for UBITh® 1 and UBITh® 2

The titers of anti-measles and anti-HBV antibodies will be compared to the maximum titer of anti-Aβ antibody in subjects to evaluate the possible correlation between the titers of anti-Aβ antibody elicited by UB-311 and anti-measles or anti-HBV antibodies in subjects.

Memory T cell response for UBITh® 1 and UBITh® 2 will be compared with titers of anti-measles or anti-HBV antibodies and anti-Aβ antibody.

6.3.2 Efficacy assessment methods

6.3.2.1 Rating scales

All scales are rated by an independent clinical psychologist and/or study nurse who has to complete the training session specifically designed for this study.

MMSE, ADAS-Cog and CDR/CDR-SB are evaluated at Weeks 1 (V1), 49 (V5) and 109 (V8). Computerized cognitive test is evaluated at Screening, Weeks 1 (V1), 25 (V4), 49 (V5), 73 (V6) and 109 (V8).

6.3.2.2 ^{18}F-AV-45 retention measurement

^{18}F-AV-45 PET is conducted at week 97 (V7) to assess the change in amyloid burden over the period of V203-AD and the extension study.

In case of scanning failure, re-injection/re-scanning of ^{18}F-AV-45 is allowed.

6.3.2.3 EEG

EEG is conducted at Screening, Weeks 1 (V1), 25 (V4), 49 (V5), 73 (V6) and 109 (V8). Five-minute eyes open and eye closed, the 3-choice vigilance task and the standard image recognition task will be performed by trained and certificated clinical personnel.

6.3.2.4 Brain volume and cortical thickness

The change of brain volume and cortical thickness is assessed by MRI imaging. MRI is scheduled at Screening, Week 13 (V3) and Week 97 (V7).

6.3.2.5 Neurodegenerative biomarkers

The level of different neurodegenerative biomarkers including $A\beta_{40}$, $A\beta_{42}$, tau, NFH, NFL, GFAP and UCHL1 is measured at Week 1 (V1), Week 49 (V5), Week 97 (V7) and Week 109 (V8).

6.4 Measures to protect blinding of this trial

In order to protect blinding of V203-AD study while it's still ongoing, study drugs for this extension study will be labelled with individual subject number. In the event that an adverse effect is considered serious and related to the study drug, and knowing the assignment is essential for treating the subject, the investigator is allowed to contact UNS or CRO to call IVRS/IWRS from V203-AD study to obtain the treatment code of that individual subject. If the treatment assignment is unblinded, the investigator must notify UNS in writing and document the course of the events in the CRF.

7 ASSESSMENT OF SAFETY

7.1 Safety Endpoints

- Local tolerability at the injection site
- Amyloid-related imaging abnormalities (ARIA) including vasogenic edema and/or sulcal effusion (ARIA-E) and hemosiderin deposits (ARIA-H), such as microhemorrhage and superficial siderosis.
- Other adverse events and serious adverse events
- Vital signs
- Physical examination
- 12-lead Electrocardiogram (ECG)
- Laboratory tests: hematology, clinical chemistry, and inflammatory parameters

7.1.1 Local tolerability

Local tolerability at injection site will be evaluated by the investigator at 30-60 minutes post-injection at Weeks 1 (V1), 5 (V2), 13 (V3), 49 (V5) and 97 (V7). The subjects will record injection site reactions happening between 1 hour post-injection and 7 days post-injection in the patient diary (see Section 7.3). Subjects will be instructed not to rub or otherwise tamper with their injection site.

7.1.2 Clinical safety

Clinical safety will be assessed by physical examination and vital signs (including temperature, respiratory rate, heart rate, blood pressure, and body weight) at screening and at every visit throughout the study (V1 to V8). Neurology examination and vital signs will be assessed again 30-60 minutes after study drug injection at Weeks 1 (V1), 5 (V2), 13 (V3), 49 (V5) and 97 (V7).

7.1.3 Adverse event collection

Adverse events and serious adverse events will be collected from the time of signing informed consent form and then at each visit until the end of the study.

7.1.4 ECG

A 12-lead ECG record is performed at Screening and at Weeks 49 (V5) and 109 (V8). The 12-lead ECGs should be performed after at least 10 minutes in supine position. The electrodes are to be positioned at the same place for each ECG recording.

Both traces will be analyzed in comparison with the screening recorded trace at the end of the study. The original trace is kept as source data. In the CRF the assessment “normal”, “abnormal-clinically significant”, or “abnormal- not clinically significant” as determined by the investigator, is collected.

7.1.5 MRI

MRI is performed at Screening and at Weeks 13 (V3) and 97 (V7) to monitor ARIA that may be induced by amyloid-modifying therapy. If a subject's last MRI scan in V203-AD study is within 3 months before the screening visit of this extension study, an MRI is not required for screening. The data of last MRI scan from V203-AD can be used for eligibility/safety evaluation in the extension study.

7.1.6 Safety laboratory

The following laboratory data are collected:

- Hematology: complete blood count including differential cell count and absolute neutrophil count at Screening, Weeks 1 (V1), 5 (V2), 13 (V3), 49 (V5), 97 (V7) and 109 (V8).
- Clinical chemistry: HbA1c at Screening; glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin at Screening, Weeks 1 (V1), 5 (V2), 13 (V3), 49 (V5), 97 (V7) and 109 (V8).
- Inflammatory parameters: CRP and ESR at Screening, and at Weeks 5 (V2), 49 (V5) and 109 (V8); TNF-α, IL-6, and IL-8 at Weeks 1 (V1), 5 (V2) and 109 (V8).

For visits during which UB-311 or placebo is scheduled to be administered (V1, V2, V3, V5 and V7), blood samples will be collected before the treatment.

7.2 Safety Instructions

7.2.1 Local tolerability

In the case where the investigator or the subject recognizes any signs of local intolerability, this should be recorded on the AE form in the CRF.

7.2.2 Monitoring of ARIA

Because vasogenic edema and other amyloid-related imaging abnormalities (ARIA) have been reported in clinical trials with multiple therapeutic avenues to lower Aβ burden in AD, subjects enrolled in this study will be followed for any suspected vasogenic edema (i.e. with symptoms and/or signs of headache, loss of coordination [ataxia], weakness or decreasing levels of consciousness) or ARIA. All Principal Investigators should be notified of the possible occurrence of ARIAs and the measures to be taken.

The detailed procedures of MRI are described in a separate imaging manual by a Central Imaging Corelab.

7.3 Adverse Events Recording

During the scheduled visits, adverse events should be collected by means of standard questions (For example: Have you had any health problems since the previous visit?). Spontaneously reported

and/or observed adverse events and the responses to the questions should be recorded on the CRF with information about the degree of seriousness and any action taken.

The patient diary will be used to record injection site reactions happening between 1 hour post-injection and 7 days post-injection. (Please also refer to the Injection Reaction Plan to acquire necessary information).

All adverse events are to be coded to a "Preferred Term" and primary "System-Organ Class" using the Medical Dictionary for Regulatory Activities (MedDRA). AEs are reported and graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 or later.

7.4 Adverse Events Monitoring

Adverse events will be monitored by Contract Research Organization (CRO) based on its Monitoring Plan. All events will be managed and reported, and included in the final clinical study report.

7.5 Definitions of Adverse Event and Serious Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject during the participation of the study, whether or not considered related to the medicinal product. An AE can therefore be any new or exacerbated unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease. The occurrence does not necessarily have to have a causal relationship with the treatment.

A priori, efficacy endpoints as specified in the protocol will not be considered as AEs except if, because of the course or severity or any other features of such events, the investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition.

Unexpected adverse drug experience is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigative plan or elsewhere in the current application, as amended. "Unexpected", as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator's brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death or,
- Is life-threatening or,

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization or,
- Results in persistent or significant disability/incapacity or,

- Is a congenital anomaly/birth defect or,
- Is a medically important event:

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

An adverse event fulfilling any one or more of these criteria should be reported as a serious adverse event, irrespective of the dose of drug given, and even if it is the result of an interaction or drug abuse.

A distinction should be drawn between serious and severe adverse events. The term 'severe' is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as 'serious,' which is based on subject's event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.6 Recording and Reporting of Adverse Event

All AEs and SAEs, regardless of seriousness or relationship to study drug(s), spanning from the first visit planned in the Clinical Trial Protocol/signature of the informed consent form up to the last (post treatment follow-up) visit, are to be reported and recorded on the corresponding page(s) or screen(s) included in the CRF.

Laboratory, vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

The investigator may be asked to provide photocopies of the medical records for completing the AE or SAE report. The medical records submitted to the relevant parties will conceal the subjects' names. It is the responsibility of the investigator to report AEs or SAEs by diagnosis terminologies, if possible. When the diagnosis is possible for the reported AE or SAE, no signs and symptoms used to establish that particular diagnosis should be reported.

The investigator will be asked to determine the severity and causality of each AE and SAE based on the investigator's clinical judgment. Adverse event reporting begins from date of consent and ended on the last day of the study period. The intensity of the AEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 as follows:

Severity of AE	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate

	instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Activities of Daily Living (ADL):

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The investigator makes a judgment regarding whether or not the AE is related to study drug, using the definitions below. The investigator is to evaluate any changes in laboratory values and make a determination as to whether or not the change is clinically important and whether or not the changes are related to study drug. However, even if the investigator determines there is no relationship to the study drug, the AE or clinically significant laboratory abnormality must still be recorded in the CRF along with the investigator's assessment of relationship as follows:

Relationship	Description
Unrelated	The AE must definitely have been caused by the subject's clinical state, or the study procedure/conditions (i.e. it had no association with the study drug)
Unlikely	The temporal association between the AE and the study drug was such that the study drug was not likely to have any reasonable association with AE.
Possible	The AE followed a reasonable temporal sequence from the time of drug administration, but could have been produced by the subject's clinical state or the study procedures / conditions.
Probable	The AE followed a reasonable temporal sequence from the time of study drug administration, abated upon discontinuation of the study drug and could not be reasonably explained by the known characteristics of the subject's clinical state.
Definite	The AE followed a reasonable temporal sequence from the time of study drug administration, abated upon discontinuation of the study drug and reappeared when the study drug is introduced.

It is usually important for the investigators to take information of underlying diseases, concomitant drugs, temporal relationship of the onset of the event to the time of dosing the study medication, and re-challenging outcomes, into account when making a causal relation decision.

It is the investigators' responsibility to follow proactively the outcome of each AE/SAE until resolution or stabilization of the condition or lost of follow-up.

Whether or not related to the study medication, all SAEs which happen during the study must be reported to the sponsor (UNS) and the CRO within the time frame (within 24 hours beginning from the investigator's knowledge of the event).

An Adverse Event Form should be completed for all SAEs and forwarded to the CRO/sponsor within 24 hours. When new significant information is obtained as well as when outcome of an event

is known, the investigator should inform the CRO/sponsor. In applicable cases, sponsor may request a letter from the investigator summarizing events related to the case. Investigator should follow subjects as far as possible until an outcome to the events is known.

The SAE/SUSAR (Suspected Unexpected Serious Adverse Reaction) will be reported to the regulatory authority and the Institutional Review Board (IRB) according to the Good Clinical Practice (GCP), regulatory, and IRB requirements. A SUSAR is defined as the SAE with the nature and severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unapproved investigational medicinal product or package insert for an approved medicinal product). The investigator is responsible to communicate details of medical emergencies in trial subjects to the IRB. In case of a SAE/SUSAR results in death or a life-threatening event, the investigator should notify IRB at the assigned institution via a written document as soon as possible within 7 days of the initial recognition (followed by completing report within 8 days) and the other SAE/SUSARs within 15 days. Sponsor/CRO is responsible to inform the events to the regulatory authorities within the same time frame.

7.7 Follow-up

The investigator should take all appropriate measures to ensure the safety of the subjects; notably he/she should follow up the outcome of any AEs (clinical signs, laboratory values or other, etc.) until the return to normal or consolidation of the subject's condition.

In case of any SAE, the subject must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the subject has left the clinical trial.

In case of any SAE brought to the attention of the investigator at any time after the initiation of clinical trial and considered by him/her to be caused by the study drug with a reasonable possibility, this should be reported to the sponsor or the sponsor's delegate within the time frame beginning from the investigator's knowledge of the event.

7.8 Obligation of the Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug to the health authorities, IRBs as appropriate and to the investigators.

In addition, the sponsor may report in an expedited manner all SAEs that are expected and at least reasonably related to the study drug to the authorities, according to local regulations.

The sponsor will report all safety observations made during the conduct of the trial in the clinical study report (CSR).

8 STUDY PROCEDURES

8.1 Study Visits

The study consists of a screening period (up to 6 weeks), a treatment period (96 weeks) with 7 visits, and a follow-up period (12 weeks). For V2 (Week 5) and V3 (Week 13), a time frame of ± 3 days is acceptable using the day of V1 as reference (Day 1), i.e. if one visit date is changed, the next visit should take place according to the original schedule. For V4 (Week 25) to V8 (Week 109), a time frame of ± 14 days is acceptable using the day of V1 as reference. Out of visit/dosing window and missing visit/dose are considered as protocol deviations.

8.1.1 The Screening visit (-42 ≤ Day ≤ -1)

The Screening visit may take place no more than 42 days prior to V1. The subject receives verbal information concerning the aims and methods of the study, its constraints and risks, and the study duration. The written informed consent must be signed by the subject, the subject's caregiver, and the investigator prior to any investigations. No screening procedures and assessments can be performed until the subject and the caregiver are fully informed of the study and sign the inform consent. Subjects, who are diagnosed with a medical condition during the screening process will be notified and referred for medical care.

This visit includes:

- Informed consent from the subject and the study caregiver
- Inclusion/Exclusion criteria
- Demographics (age and gender)
- Complete medical history and concomitant diseases (general medical history: up to 30 days prior to screening visit; neurological and psychiatric: within 1 year prior to screening visit; surgery / Procedure: within 10 years prior to screening visit; other cancer history: life time base)
- Concomitant and previous medication (within the last 3 months)
- Record of AEs and SAEs
- Physical examination and height
- Vital signs, including temperature, respiratory rate, heart rate, blood pressure, and body weight
- Structural MRI scanning (If a subject's last MRI scan in V203-AD study is within 3 months before the screening visit of this extension study, an MRI is not required for screening.)
- 12-lead ECG
- Computerized cognitive test (two practices will be performed before the real test)
- EEG
- Blood collection for testing of:
  - CRP and ESR

- Clinical chemistry (HbA1c, glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin)
- Hematology (complete blood count including differential cell count and absolute neutrophil count)
- Anti-measles and anti-HBV antibodies
- Memory T cell response for UBITh® 1 and UBITh® 2

8.1.2 Visit 1 (Week 1, Day 1)

This visit (V1) should be scheduled within 6 weeks after S1 and includes:

- Verification of Inclusion/Exclusion criteria and check for eligibility
- Survey instruments
  - MMSE
  - CDR-SB
  - ADAS-Cog
  - Computerized cognitive test
- EEG
- Record of AEs and SAEs
- Record of the use or change of any concomitant medications
- Physical examination
- Vital signs, including temperature, respiratory rate, heart rate, blood pressure, and body weight
- Blood collection for: (before the UB-311 injection)
  - Anti-Aβ, anti-$A\beta_{1-42}$ monomer and anti-$A\beta_{1-42}$ oligomer antibodies
  - TNF-α, IL-6, and IL-8
  - Clinical chemistry (glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin)
  - Hematology (complete blood count including differential cell count and absolute neutrophil count)
  - Neurodegenerative biomarkers ($A\beta_{40}$, $A\beta_{42}$, tau, NFH, NFL, GFAP and UCHL1)
- Injecting study drug
- Injection site assessments, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

8.1.3 Visit 2 (Week 5, Day 29)

This visit (V2) should be scheduled 4 weeks ± 3 days after V1 and includes:

- Record of AE and SAE
- Record of the use or change of any concomitant medications
- Physical examination
- Vital signs, including temperature, respiratory rate, heart rate, blood pressure, and body weight
- Blood sampling for: (before the UB-311/placebo injection)
  - Anti-Aβ, anti-$A\beta_{1-42}$ monomer and anti-$A\beta_{1-42}$ oligomer antibodies
  - CRP, ESR, TNF-α, IL-6, and IL-8
  - Clinical chemistry (glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin)
  - Hematology (complete blood count including differential cell count and absolute neutrophil count)
- Injecting study drug
- Injection site assessments, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

8.1.4 Visit 3 (Week 13, Day 85)

This visit (V3) should be scheduled 12 weeks ± 3 days after V1 and includes:

- Structural MRI scanning (should be scheduled < 14 days before the injection of study drug)
- Record of AEs and SAEs
- Record of the use or change of any concomitant medications
- Physical examination
- Vital signs, including temperature, respiratory rate, heart rate, blood pressure, and body weight
- Blood collection for: (before the UB-311/placebo injection)
  - Anti-Aβ, anti-$A\beta_{1-42}$ monomer and anti-$A\beta_{1-42}$ oligomer antibodies
  - Clinical chemistry (glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin)
  - Hematology (complete blood count including differential cell count and absolute neutrophil count)
  - Anti-measles and anti-HBV antibodies
  - Memory T cell response for UBITh® 1 and UBITh® 2
- Injecting study drug
- Injection site assessment, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

8.1.5 Visit 4 (Week 25, Day 169)

This visit (V4) should be scheduled 24 weeks ± 14 days after V1 and includes:

- Record of AEs and SAEs
- Record of the use or change of any concomitant medications
- Physical examination
- Vital signs, including temperature, respiratory rate, heart rate, blood pressure, and body weight
- EEG
- Computerized cognitive test

8.1.6 Visit 5 (Week 49, Day 337)

This visit (V5) should be scheduled 48 weeks ± 14 days after V1 and includes:

- 12-lead ECG
- Survey instruments
  - MMSE
  - CDR-SB
  - ADAS-Cog
  - Computerized cognitive test
- EEG
- Record of AEs and SAEs
- Record of the use or change of any concomitant medications
- Physical examination
- Vital signs, including temperature, respiratory rate, heart rate, blood pressure, and body weight
- Blood collection for: (before the UB-311 injection)
  - Anti-Aβ, anti-$A\beta_{1\text{-}42}$ monomer and anti-$A\beta_{1\text{-}42}$ oligomer antibodies
  - CRP and ESR
  - Clinical chemistry (glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin)
  - Hematology (complete blood count including differential cell count and absolute neutrophil count)
  - Neurodegenerative biomarkers ($A\beta_{40}$, $A\beta_{42}$, tau, NFH, NFL, GFAP and UCHL1)
- Injecting study drug

- Injection site assessment, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

8.1.7 Visit 6 (Week 73, Day 505)

This visit (V6) should be scheduled 72 weeks ± 14 days after V1 and includes:

- Record of AEs and SAEs
- Record of the use or change of any concomitant medications
- Physical examination
- Vital signs, including temperature, respiratory rate, heart rate, blood pressure, and body weight
- EEG
- Computerized cognitive test

8.1.8 Visit 7 (Week 97, Day 673)

This visit (V7) should be scheduled 96 weeks ± 14 days after V1 and includes:

- Structural MRI scanning (should be scheduled < 14 days before the injection of study drug)
- ^{18}F-AV-45 PET scanning (a time frame of ±14 days is acceptable)
- Record of AEs and SAEs
- Record of the use or change of any concomitant medications
- Physical examination
- Vital signs, including temperature, respiratory rate, heart rate, blood pressure, and body weight
- Blood sampling for: (before the UB-311 injection)
  - Anti-Aβ, anti-$A\beta_{1-42}$ monomer and anti-$A\beta_{1-42}$ oligomer antibodies
  - Clinical chemistry (glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin)
  - Hematology (complete blood count including differential cell count and absolute neutrophil count)
  - Neurodegenerative biomarkers ($A\beta_{40}$, $A\beta_{42}$, tau, NFH, NFL, GFAP and UCHL1)
- Injecting study drug
- Injection site assessment, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

8.1.9 Visit 8 (Week 109, Day 757)

This visit (V8) should be scheduled 108 weeks ± 14 days after V1 and includes:

- 12-lead ECG
- Survey instruments
  - MMSE
  - CDR-SB
  - ADAS-Cog
  - Computerized cognitive test
- EEG
- Record of AEs and SAEs
- Record of the use or change of any concomitant medications
- Physical examination
- Vital signs, including temperature, respiratory rate, heart rate, blood pressure, and body weight
- Blood sampling for:
  - Anti-Aβ, anti-$A\beta_{1-42}$ monomer and anti-$A\beta_{1-42}$ oligomer antibodies
  - CRP, ESR, TNF-α, IL-6, and IL-8
  - Clinical chemistry (glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin)
  - Hematology (complete blood count including differential cell count and absolute neutrophil count)
  - Neurodegenerative biomarkers ($A\beta_{40}$, $A\beta_{42}$, tau, NFH, NFL, GFAP and UCHL1)
  - Anti-measles and anti-HBV antibodies
  - Memory T cell response for UBITh® 1 and UBITh® 2

8.2 Events and Time Schedule

Visit	S	V1	V2	V3	V4	V5	V6	V7	V8/ET
Week	-6~-1	1/BL	5	13	25	49	73	97	109/ET
Day	-42~-1	1	29±3	85±3	169±14	337±14	505±14	673±14	757±14
Vaccination/injection site assessment/ Neurology/vital signs[1]		X	X	X		X		X	
ICF, medical history & concomitant disease, demographics	X								
Incl./excl. criteria	X	X							
ECG	X					X			X
MRI[2]	X			X				X	X**
^{18}F-AV-45 PET[3]								X	X**
MMSE, CDR-SB and ADAS-Cog		X				X			X
Computerized cognitive test	X	X			X	X	X		X
EEG	X	X			X	X	X		X
AE/SAE	X	X	X	X	X	X	X	X	X
Previous and concomitant medicines	X	X	X	X	X	X	X	X	X
PE[4]/vital signs	X	X	X	X	X	X	X	X	X
Anti-Measles antibody	X			X*					X
Anti-HBV surface antibody	X			X*					X
Memory T cell response test	X			X*					X
Clinical chemistry & hematology[5]	X	X*	X*	X*		X*		X*	X
Inflammatory[6]	X	X*	X*			X*			X
Anti-Aβ Ab level in serum		X*	X*	X*		X*		X*	X
Anti-$A\beta_{1-42}$ monomer & oligomer Antibodies		X*	X*	X*		X*		X*	X
Neurodegenerative biomarkers ($A\beta_{40}$, $A\beta_{42}$, Tau, NFL, NFH, GFAP and UCHL1)		X*				X*		X*	X

BL=baseline; ET=early termination; MRI=structure MRI

1. 30-60 minutes after injection. Vital sign: not need to measure body weight.
2. If a subject's last MRI scan in V203-AD study is within 3 months before the screening visit of this extension study, an MRI is not required for screening. The data of last MRI scan from V203-AD can be used for eligibility/safety evaluation in the extension study. For V3 (Week 13) and V7 (Week 97), MRI should be scheduled <14 days before the injection of study drug.
3. A time frame of ±14 days is acceptable for ^{18}F-AV-45 PET scan.
4. Including height (for S1 only)
5. Clinical chemistry: HbA1c (for S1 only), glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin at S1 and every visit throughout the study (V1 to V8); Hematology: complete blood count including differential cell count and ANC at S1and every visit throughout the study (V1 to V8).
6. Inflammatory parameters: CRP and ESR: for S1, V2 (Week 5), V5 (Week 49) and V8 (Week 109); TNF-α, IL-6, and IL-8: for V1 (Week 1), V2 (Week 5) and V8 (Week 109).

* Blood specimens should be drawn before the UB-311/Placebo injection.
** For early termination visit only.

8.3 Blood Sample Collection

For visits that UB-311 or placebo is scheduled to be administrated (V1, V2, V3, V5and V7), blood samples will be collected before the treatment.

At Screening, V1, V2, V3, V5, V7 and V8/ET, different amount of blood will be collected in plain tube, SST II tube, NaF tube, EDTA or heparin tube. The details are described in the central laboratory's handbook.

9 STATISTICS

The material of this section is the basis for the Statistical Analysis Plan (SAP) for the study. The SAP may be revised during the study to accommodate Clinical Trial Protocol amendments and to make changes to adapt to unexpected issues in study execution and data that may affect planned analyses.

9.1 Analysis Variables

9.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value before the first injection of UB-311 in the extension study.

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

Disease characteristics including:

- Disease duration (years): (date of informed consent – date of diagnosis)/365.25
- Baseline scores of MMSE, CDR-SB, ADAS-Cog and computerized cognitive test

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

The baseline safety data of clinical chemistry and hematology, CRP, ESR, TNF-α, IL-6, IL-8, and number of microhemorrhages in the brain will also be summarized.

9.1.2 Immunogenicity variables

The level of anti-Aβ antibodies is one of the primary endpoints and is assessed at Week 1 (V1), Week 5 (V2), Week 13 (V3), Week 49 (V5), Week 97 (V7) and Week 109 (V8). The one-sided 95% confidence interval (CI, right side) from all visits (V1 to V13) for subjects in Arm 3 (placebo group) of V203-AD study 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 first injection of UB-311.

9.1.3 Efficacy variables

9.1.3.1 Rating scales

MMSE, CDR-SB and ADAS-Cog are rated at Week 1 (V1), Week 49 (V5) and Week 109 (V8), while computerized cognitive test is assessed at the Screening visit, Week 1 (V1), Week 25 (V4),

Week 49 (V5), Week 73 (V6) and Week 109 (V8). Although the scores of two practices of computerized cognitive test at screening will be recorded, only the score of the real test will be used for data analysis. 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.

9.1.3.2 ^{18}F-AV-45 retention

^{18}F-AV-45 PET scanning is performed within ±14 days of V7 date. No procedure for handling missing assessments will be applied if there is a missing value.

9.1.4 Safety variables

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

- Local tolerability at injection site
- Amyloid-related imaging abnormalities (ARIA) including vasogenic edema and/or sulcal effusion (ARIA-E) and hemosiderin deposits (ARIA-H), including microhemorrhage and superficial siderosis
- Vital signs
- Physical examination
- 12-lead ECG
- Laboratory tests: hematology, clinical chemistry (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)

9.2 Analysis Populations

9.2.1 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 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.

9.2.2 Safety population

The safety population is the total treated population defined as all subjects 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.

9.2.3 Disposition of subjects

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
- Enrolled subjects: subjects who are enrolled in the extension study
- The safety population (as defined in Section 9.2.2)
- The mITT population (as defined in Section 9.2.1)
- The PP population (as defined in Section 9.2.1)

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

9.3 Statistical Methods

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

Categorical data will be summarized 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.

All statistical tests will be two-sided at the alpha level of 0.05.

9.3.1 Demographic and baseline characteristics

9.3.1.1 Subject demographic characteristics, medical history and diagnoses

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

Pathologies associated with past medical and surgical history will be classified into primary system organ classes and preferred terms using MedDRA and will be summarized using counts and percentages. The primary system organ classes and preferred terms will be sorted in decreasing order of frequency.

9.3.1.2 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 Screening visit and prior to the first administration of UB-311 at Week 1 (V1).
- 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.

9.3.2 Treatment tolerability and compliance

The overall treatment tolerability of UB-311 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:

$100\% \times (A+B_1+C+D) / (A+B_1+B_2+C+D)$

where

A: number of administered doses of completers

B_1: number of administered doses of subject(s) who drops out due to drug-related AE(s)

B_2: 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)

9.3.3 Analysis of immunogenicity variable

Immunogenicity analyses will be performed on the mITT and PP populations. The change in antibody level will be analyzed by a repeated-measures mixed-effects model.

9.3.4 Analysis of efficacy variables

Efficacy analyses will be performed on the mITT and PP populations. Descriptive statistics will be provided for all continuous variables at the scheduled visits. Continuous variables with repeated measures will be analyzed using a mixed-effects model.

9.3.5 Analysis of safety data

The review of safety and tolerance will be performed on the safety population as defined in section 9.3.2 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 UB-311 in the extension study.
- The post-treatment period is defined as the time from after the first dose of UB-311 to the end of the study.

9.3.5.1 Analysis of adverse event

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 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 (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 in the study.

Adverse events leading to treatment discontinuation

TEAEs leading to treatment discontinuation will be summarized and presented as number and percentage of subjects in the study.

Local tolerability at injection site

The number and percentage of subjects with reaction at injection site will be summarized and presented.

Vasogenic brain edema and amyloid imaging related abnormalities

The number and percentage of subjects with amyloid-related imaging abnormalities (ARIA) will be summarized and presented.

9.3.5.2 Analysis of laboratory variables

The summaries will include subjects in the safety population who have 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 UB-311 injection.

Clinical laboratory values will be converted to standard international units. Descriptive statistics will be used to summarize the laboratory results and the changes from baseline by scheduled visit.

9.3.5.3 Analysis of vital sign variables

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.

9.3.5.4 Analysis of 12-lead ECG status

Only ECG status (i.e. normal or abnormal (clinically significant or not clinically significant)) will be reported.

9.3.5.5 Reason for withdrawal

Reason for withdrawal will be tabulated.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Responsibility of the Investigator(s)

The Investigator(s) undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and the applicable regulatory requirements.

The investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the sponsor (including security rules). The investigator agrees to provide reliable data and all information requested by the clinical trial protocol in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the patient's data to be transferred.

The investigator may appoint such other individuals, as he/she may deem appropriate as co-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All co-investigators shall be appointed and listed in a timely manner. The co-investigators will be supervised by and work under the responsibility of the Investigator. The investigator will provide them with a copy of the clinical trial protocol and all necessary information.

10.2 Responsibility of the Sponsor

The sponsor of this clinical trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the case report forms. Thus, the main duty of the sponsor or sponsor’s delegate is to help the investigator and the sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the sponsor or sponsor’s delegate to review study progress, investigator and subject compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but are not limited to review of the following aspects: subject informed consent, subject recruitment and follow-up, SAE documentation and reporting, AE documentation, study drug allocation, subject compliance with the study drug regimen, study drug accountability, concomitant therapy use and quality of data.

10.3 Source Document Requirements

According to the ICH guidelines for GCP, the sponsor or sponsor’s delegate must check the case report form (CRF) entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the sponsor’s duly authorized personnel, the independent ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRF (eg, subject's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality rules).

10.4 Use and Completion of Case Report Forms (CRFs) and Additional Request

It is the responsibility of the investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the sponsor to record (according to sponsor instructions) all observations and other data pertinent to the clinical investigation. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. Should a correction be made, the correction will be recorded in the CRF. An audit trail will allow to identify the modification.

11 ETHICS

11.1 Declaration of Helsinki and Ethical Review

The study will be performed in accordance with the principles stated in the Declaration of Helsinki. The institutional review board (IRB) must approve the study protocol and informed consent form before the enrollment of subjects. The views of the IRB should be dated and filed. The names and titles of those who attend the IRB meeting should be attached. After receiving the approval letter from the IRB, the investigators have the responsibility to forward the copy of the approved letter to UNS before the commencement of the clinical trial.

The investigator is responsible for informing the IRB of any serious adverse events and/or major amendments to the protocol as per local requirements. The investigator should file all correspondence with the IRB.

11.2 Patient Information and Consent

The investigator will ensure that the subject and his/her caregiver (must be a family member) are given full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the clinical trial. Subjects and their caregivers must also be informed that they are free to discontinue their participation in the clinical trial at any time. The investigator must see the signed informed consent before enrolment.

The subjects should have a copy of the ICF. If any modifications are to be made according to local requirements, the new version must be approved by UNS and IRB as well.

11.3 Patient Data Protection

In the CRFs, all patients should be identified by number, initials, date of birth and sex. The investigator is responsible for keeping a name list of all patients including patients' numbers, full names and last known address.

The subjects will be informed in ICF about the possibility of audits by authorized representatives of the UNS and/or regulatory authorities in which case a review of those parts of the hospital records relevant to the study may be required. However, the investigator will follow all applicable privacy laws in order to protect a subject's privacy and confidentiality.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Management

The monitor and the investigator will ensure that the data are correctly and legibly recorded on the CRF. Monitors are responsible for the data editing. All data should be verified before data management. Any corrections should be verified and recorded by the investigator.

The sponsor or its delegate will be responsible for data management of the trial. The responsibilities include database setup, entry screen generation, data entry and verification, data query/resolution, data cleanup, and data lock. Database will be converted into SAS dataset for statistical analysis.

12.2 Record Retention in Study Sites

The investigator must maintain all confidential study documentation, and take measures to prevent accidental or premature destruction of these documents.

It is recommended that the investigator retain the study documents at least 2 years after the approval of a marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The investigator must notify the sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the investigator's personal situation is such that archiving can no longer be ensured by him/her, the investigator shall inform the sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

13 FINANCING AND INSURANCE

The sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the sponsor does not relieve the investigator and the collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the IRB or health authorities in countries requiring this document.

14 PUBLICATION POLICY

UNS follows local regulatory requirements relating to clinical trial registration and disclosure of results.

UNS commits to seek publication of results of its completed applicable clinical trials on any marketed product in the peer-reviewed scientific literature, regardless of trial outcome. UNS supports recognized standards concerning authorship and publication.

UNS will provide final statistical reports of protocol-derived outcomes to external authors. UNS reserves the right to review and comment on draft abstracts, manuscripts, presentations and other communications by external investigators regarding UNS-sponsored trials, prior to submission or public disclosure, in order to protect intellectual property and confidential information. As study sponsor, UNS does not approve or veto such publications.

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