

## CLINICAL TRIAL PROTOCOL

---

Investigational Product:  
UBITh<sup>®</sup> AD Immunotherapeutic Vaccine (UB-311)

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

---

Protocol Number:  
V203-AD

***Confidential***

Version: 5.0  
Date: 28-Nov-2017

---

This document contains confidential information and is the property of United Neuroscience Ltd. (UNS). The receiver(s) of this document understood and agreed that this document is not to be disclosed to any unauthorized third party without written agreement issued by the sponsor. The need to disclose certain information contained in this document for the purpose of obtaining informed consent from potential subjects or his/her legally acceptable representative(s) of this study will be considered as exceptions.

**Principal Investigators:**

Dr. Pei-Ning Wang (王培寧醫師)

Department of Neurology,  
Taipei Veterans General Hospital, Taipei, Taiwan

Dr. Ming-Jang Chiu (邱銘章醫師)

Department of Neurology,  
National Taiwan University Hospital, Taipei, Taiwan

Dr. Chin-Chang Huang (黃錦章醫師)

Department of Neurology,  
Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan

Dr. Chiung-Chih Chang (張瓊之醫師)

Department of Neurology,  
Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

**Sponsor:**

愛爾蘭商聯腦科學股份有限公司台灣分公司

United Neuroscience Ltd., Taiwan Branch (Ireland)  
Taipei, Taiwan

**Product authorized by:**

愛爾蘭商聯腦科學股份有限公司

United Neuroscience Ltd. (UNS)

**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.**

<b>Name</b>	<b>Affiliation</b>	<b>Signature</b>	<b>Date</b>
<hr/>	<hr/>	<hr/>	<hr/>
<hr/>	<hr/>	<hr/>	<hr/>

**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.**

<b>Name</b>	<b>Affiliation</b>	<b>Signature</b>	<b>Date</b>
<hr/>	<hr/>	<hr/>	<hr/>
<hr/>	<hr/>	<hr/>	<hr/>

**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.**

<b>Affiliation</b>	<b>Name</b>	<b>Position</b>	<b>Signature</b>	<b>Date</b>
United Neuroscience Ltd., Taiwan				

**TABLE OF CONTENTS**

**TABLE OF CONTENTS** ..... i

**LIST OF ABBREVIATIONS**..... vi

**SYNOPSIS**..... x

**1 INTRODUCTION AND RATIONALE** ..... 1

**2 OBJECTIVES**..... 4

**3 TRIAL DESIGN** ..... 4

**3.1 Description of the Protocol**..... 4

**3.1.1 Screening Period**..... 4

**3.1.2 Treatment Period**..... 5

**3.1.3 Follow-up Period**..... 5

**3.2 Endpoints**..... 5

**3.2.1 Primary**..... 5

**3.2.2 Secondary**..... 5

**3.3 Description of Blinding Methods** ..... 6

**3.4 Description of Randomization** ..... 6

**3.5 Stopping Rules** ..... 6

**4 SELECTION AND WITHDRAWAL OF SUBJECTS** ..... 7

**4.1 Number of Subjects**..... 7

**4.2 Inclusion Criteria** ..... 7

**4.3 Exclusion Criteria** ..... 8

**4.4 Subject Withdrawal Criteria**..... 9

**5 TREATMENT OF SUBJECTS** ..... 11

**5.1 Description of Study Drug**..... 11

**5.2 Dosing Regimens and Rationale** ..... 11

<b>5.3</b>	<b>Handling of Study Drug .....</b>	<b>11</b>
5.3.1	<i>Packing and Labelling.....</i>	<i>11</i>
5.3.2	<i>Storage.....</i>	<i>12</i>
<b>5.4</b>	<b>Drug Accountability .....</b>	<b>12</b>
<b>5.5</b>	<b>Concomitant Medicines.....</b>	<b>12</b>
5.5.1	<i>Permitted Medicines.....</i>	<i>12</i>
5.5.2	<i>Prohibited Medicines .....</i>	<i>12</i>
<b>5.6</b>	<b>Subject Compliance .....</b>	<b>13</b>
<b>6</b>	<b>ASSESSMENT OF INVESTIGATIONAL PRODUCT.....</b>	<b>14</b>
<b>6.1</b>	<b>Immunogenicity .....</b>	<b>14</b>
6.1.1	<i>Anti-A<math>\beta</math> antibody measurement.....</i>	<i>14</i>
6.1.2	<i>Response rate.....</i>	<i>14</i>
<b>6.2</b>	<b>Safety.....</b>	<b>14</b>
<b>6.3</b>	<b>Efficacy.....</b>	<b>14</b>
6.3.1	<i>Evaluation variables .....</i>	<i>14</i>
6.3.2	<i>Efficacy assessment methods.....</i>	<i>15</i>
<b>6.4</b>	<b>Measures to protect blinding of this trial.....</b>	<b>15</b>
<b>7</b>	<b>ASSESSMENT OF SAFETY.....</b>	<b>16</b>
<b>7.1</b>	<b>Safety Endpoints .....</b>	<b>16</b>
7.1.1	<i>Local tolerability .....</i>	<i>16</i>
7.1.2	<i>Clinical safety.....</i>	<i>16</i>
7.1.3	<i>Adverse event collection.....</i>	<i>16</i>
7.1.4	<i>ECG.....</i>	<i>16</i>
7.1.5	<i>MRI.....</i>	<i>17</i>
7.1.6	<i>Safety laboratory.....</i>	<i>17</i>

<b>7.2</b>	<b>Safety Instructions .....</b>	<b>17</b>
7.2.1	<i>Local tolerability .....</i>	<i>17</i>
7.2.2	<i>Monitoring of ARIA.....</i>	<i>17</i>
<b>7.3</b>	<b>Adverse Events Recording .....</b>	<b>18</b>
<b>7.4</b>	<b>Adverse Events Monitoring.....</b>	<b>18</b>
<b>7.5</b>	<b>Definitions of Adverse Event and Serious Adverse Event .....</b>	<b>18</b>
<b>7.6</b>	<b>Recording and Reporting of Adverse Event.....</b>	<b>19</b>
<b>7.7</b>	<b>Follow-up.....</b>	<b>21</b>
<b>7.8</b>	<b>Obligation of the Sponsor.....</b>	<b>21</b>
<b>7.9</b>	<b>Data and Safety Monitoring Board.....</b>	<b>22</b>
<b>7.10</b>	<b>Risk Management .....</b>	<b>23</b>
<b>8</b>	<b>STUDY PROCEDURES.....</b>	<b>24</b>
<b>8.1</b>	<b>Study Visits.....</b>	<b>24</b>
8.1.1	<i>The First Stage Screening (-42 &lt; Day &lt; 0) .....</i>	<i>24</i>
8.1.2	<i>The Second Stage Screening (-42 &lt; Day &lt; 0) .....</i>	<i>25</i>
8.1.3	<i>Visit 1 (Week 0, Day 0 / baseline) .....</i>	<i>25</i>
8.1.4	<i>Visit 2 (Week 4, Day 28).....</i>	<i>26</i>
8.1.5	<i>Visit 3 (Week 12, Day 84).....</i>	<i>26</i>
8.1.6	<i>Visit 4 (Week 16, Day 112).....</i>	<i>27</i>
8.1.7	<i>Visit 5 (Week 24, Day 168).....</i>	<i>27</i>
8.1.8	<i>Visit 6 (Week 28, Day 196).....</i>	<i>28</i>
8.1.9	<i>Visit 7 (Week 36, Day 252).....</i>	<i>28</i>
8.1.10	<i>Visit 8 (Week 40, Day 280).....</i>	<i>29</i>
8.1.11	<i>Visit 9 (Week 48, Day 336).....</i>	<i>29</i>
8.1.12	<i>Visit 10 (Week 52, Day 364).....</i>	<i>30</i>



8.1.13	<i>Visit 11 (Week 60, Day 420)</i> .....	31
8.1.14	<i>Visit 12 (Week 64, Day 448)</i> .....	31
8.1.15	<i>Visit 13 (Week 78, Day 546)</i> .....	32
8.2	<b>Events and Time Schedule</b> .....	<b>33</b>
8.3	<b>Blood Sample Collection</b> .....	<b>34</b>
9	<b>STATISTICS</b> .....	<b>36</b>
9.1	<b>Determination of Sample Size</b> .....	<b>36</b>
9.2	<b>Analysis Variables</b> .....	<b>36</b>
9.2.1	<i>Demographic and baseline characteristics</i> .....	36
9.2.2	<i>Immunogenicity variables</i> .....	37
9.2.3	<i>Efficacy variables</i> .....	37
9.2.4	<i>Safety variables</i> .....	37
9.3	<b>Analysis Populations</b> .....	<b>37</b>
9.3.1	<i>Efficacy populations</i> .....	37
9.3.2	<i>Safety population</i> .....	38
9.3.3	<i>Disposition of subjects</i> .....	38
9.4	<b>Statistical Methods</b> .....	<b>38</b>
9.4.1	<i>Demographic and baseline characteristics</i> .....	39
9.4.2	<i>Treatment tolerability and compliance</i> .....	39
9.4.3	<i>Analysis of immunogenicity variable</i> .....	40
9.4.4	<i>Analysis of efficacy variables</i> .....	40
9.4.5	<i>Analysis of safety data</i> .....	40
10	<b>QUALITY CONTROL AND QUALITY ASSURANCE</b> .....	<b>43</b>
10.1	<b>Responsibility of the Investigator(s)</b> .....	<b>43</b>
10.2	<b>Responsibility of the Sponsor</b> .....	<b>43</b>

10.3 Source Document Requirements .....	43
10.4 Use and Completion of Case Report Forms (CRFs) and Additional Request .....	44
11 ETHICS .....	45
11.1 Declaration of Helsinki and Ethical Review .....	45
11.2 Patient Information and Consent .....	45
11.3 Patient Data Protection .....	45
12 DATA HANDLING AND RECORD KEEPING .....	46
12.1 Data Management .....	46
12.2 Record Retention in Study Sites .....	46
13 FINANCING AND INSURANCE .....	47
14 PUBLICATION POLICY .....	48
15 REFERENCES .....	49
<b><u>APPENDIX 1: IMAGING PROTOCOL</u></b> .....	51
<b><u>1 Introduction</u></b> .....	51
<b><u>2 MRI Methods</u></b> .....	51
<b><u>3 18F-AV-45 PET Methods</u></b> .....	53
<b><u>4 Volumetric Magnetic Resonance Imaging (vMRI) for the Research Study</u></b> .....	54
<b><u>5 Resting state fMRI (rs-fMRI) for the Research Study</u></b> .....	55
<b><u>6 Reference</u></b> .....	55
<b><u>APPENDIX 2: RESEARCH STUDY PROTOCOL</u></b> .....	56

**LIST OF ABBREVIATIONS**

<b>ABBREVIATION</b>	<b>TERM</b>
A $\beta$	Amyloid $\beta$
AChE	Acetyl Cholinesterase
AD	Alzheimer’s Disease
ADAS-Cog	Alzheimer’s Disease Assessment Scale-Cognitive Subscale
ADCS-ADL	Alzheimer’s Disease Cooperative Study-Activities of Daily Living
ADL	Activities of Daily Living
AE	Adverse Event
ARWMC	Age-Related White Matter Changes
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
aPTT	Activated Partial Thromboplastin Time
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	Clinical Dementia Rating
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
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAD	Disability Assessment for Dementia
dL	Deciliter
DNA	Deoxyribonucleic Acid
DOH	Department of Health

---

DSMB	Data and Safety Monitoring Board
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e-CRF	Electronic Case Report Form
EDTA	Ethylenediamine Tetra Acetic Acid
EIA	Enzyme Immunoassay
ESR	Erythrocyte Sedimentation Rate
ET	Early Termination
FLAIR	Fluid Attenuated Inversion Recovery
fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practice
GDS-SF	Geriatric Depression Scale-Short Form
GRE	Gradient Refocused Echo
HbA1c	Glycosylated Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIS	Hachinski Ischemic Score
HIV	Human Immunodeficiency 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
IVRS/IWRS	Interactive Voice/Web Response System
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	Miligram
mITT	Modified Intention-to-treat

mL	Mililiter
mm	Milimeter
MMSE	Mini Mental State Examination
MP-RAGE	Magnetization-prepared Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
n	Number of Observations Available
NCI	National Cancer Institute
NIA-AA	National Institute on Aging–Alzheimer’s Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke, and Alzheimer’s Disease and Related Disorders Association
NMDA	N-methyl-D-aspartate
NPI	Neuropsychiatric Inventory
NTB	Neuropsychological Test Battery
NTUH	National Taiwan University Hospital
PE	Physical Examination
PET	Positron Emission Tomography
PP	Per-protocol
ROI	Region of Interest
PT	Prothrombin Time
RF	Rheumatoid Factor
rs-fMRI	Resting State fMRI
S	Screening
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SHH	Shuang Ho Hospital
SSRIs	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUVr	Standard Uptake Value Ratio
TEAE	Treatment-emergent Adverse Event
TNF- $\alpha$	Tumor necrosis factor-alpha
TVGH	Taipei Veterans General Hospital
UNS	United Neuroscience Ltd.
ULRR	Upper Limit of Reference Range
US FDA	United States, Food and Drug Administration
V	Visit
vMRI	Volumetric Magnetic Resonance Imaging
W	Week
WBC	White Blood Cells

WHO World Health Organization

---

**SYNOPSIS**

<b>PROTOCOL NUMBER</b>	V203-AD
<b>TITLE</b>	A Randomized, Double-blind, Placebo-controlled, 3-arm Parallel-group, Multicenter, Phase IIa Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of UBITH <sup>®</sup> AD Immunotherapeutic Vaccine (UB-311) in Patients with Mild Alzheimer’s Disease
<b>STUDY SITES</b>	There will be five 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
<b>STUDY OBJECTIVES</b>	<ol style="list-style-type: none"> <li>1. To assess the safety and tolerability of two regimens of UB-311;</li> <li>2. To evaluate the immunogenicity of two regimens of UB-311;</li> <li>3. To evaluate the effects of UB-311 on the changes of cognitive and functional performance over a period of 78 weeks; and</li> <li>4. To investigate whether UB-311 treatment results in changes in amyloid deposition <i>in vivo</i> by Florbetapir F18 (also known as 18F-AV-45, Eli Lilly and Company) PET imaging.</li> </ol>
<b>STUDY DESIGN</b>	<p>This is a 78-week, multicenter, randomized, double-blind, placebo-controlled Phase IIa study. Eligible subjects, 60 to 90 years old with mild Alzheimer’s disease (AD), will be further screened by 18F-AV-45 PET scan for the presence of amyloid deposition.</p> <p>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 till Week 78.</p> <p>Subjects enrolled in the Phase I trial with UB-311 will be excluded from the Phase IIa trial.</p>

<p><b>STUDY POPULATION</b></p> <p><b>Total expected number of subjects</b></p> <p><b>Inclusion criteria</b></p>	<p>Approximately 45 subjects will be enrolled to receive study treatment, approximately 15 subjects per treatment arm.</p> <p>Subjects may be included in the clinical trial only if they meet <b>all</b> of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Male or female aged between 60-90 years old;</li> <li>2. Probable Alzheimer’s disease based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria and National Institute on Aging–Alzheimer’s Association (NIA-AA) guidelines;</li> <li>3. Mini-Mental State Examination (MMSE) scores between 20 and 26 (inclusive);</li> <li>4. Clinical dementia rating (CDR) scores of 0.5 or 1;</li> <li>5. At least 6 years of education or sufficient work history (to exclude mental retardation);</li> <li>6. Visual and auditory acuity adequate for neuropsychological testing;</li> <li>7. 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;</li> <li>8. Hachinski ischemic score (HIS) <math>\leq 4</math> (original score);</li> <li>9. Geriatric Depression Scale-Short Form (GDS-SF) <math>&lt; 6</math>;</li> <li>10. Eastern Cooperative Oncology Group (ECOG) performance status 0-2;</li> <li>11. Female must either be post-menopausal (no menstrual period for <math>&gt; 1</math> 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;</li> <li>12. 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), to perform study-related AD scales and to accompany or delegate a companion with the subject to all visits. A companion needs not to be a family member (with kinship);</li> <li>13. Both patient and his/her caregiver should sign the written</li> </ol>
---	--



	<p>informed consent before undergoing any study procedures;</p> <p>14. Agree not to donate blood or blood products for transfusion during the study and for 3 months thereafter; and</p> <p>15. A positive of A<math>\beta</math> plaque on 18F-AV-45 PET by an imaging expert (confirmed during the second stage of screening per central independent review).</p>
<p><b>Exclusion criteria</b></p>	<p>Subjects will be excluded from the clinical trial for <b>any</b> of the following reasons:</p> <ol style="list-style-type: none"> <li>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 deficits or known structural brain abnormalities;</li> <li>2. Screening magnetic resonance imaging (MRI) scan with evidence of central nervous system (CNS) infection, cerebrovascular disease, infarction, or other focal lesions, or a single area of superficial siderosis, or a prior macrohemorrhage, or more than four microhemorrhages, multiple lacunes or lacunes in a critical memory structure;</li> <li>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;</li> <li>4. History of schizophrenia (DSM-V criteria);</li> <li>5. Any significant systemic illness or unstable medical condition which could lead to difficulty in complying with the protocol;</li> <li>6. History of alcohol or substance abuse or dependence within the past 2 years before screening (DSM-V criteria);</li> <li>7. History of autoimmune disease, including but not limited to ankylosing spondylitis, Sjogren’s syndrome, systemic lupus erythematosus, rheumatic arthritis, or multiple sclerosis;</li> <li>8. History of severe systemic disease that may affect a subject’s participation at the investigator’s discretion;</li> <li>9. History of anaphylaxis; other serious adverse reactions to any vaccine; or any serious allergic reactions to medications requiring treatment;</li> <li>10. Use of any prohibited medications within 4 weeks prior to</li> </ol>

	<p>screening;</p> <ol style="list-style-type: none"> <li>11. Use of any investigational drug within 4 weeks before screening;</li> <li>12. Current participation in clinical studies involving ADAS-Cog, MMSE, ADCS-ADL, CDR-SB, or NPI being collected more than one time per score per year;</li> <li>13. Previous exposure to any anti-A<math>\beta</math> immunotherapy;</li> <li>14. 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);</li> <li>15. Received blood or blood derivatives treatment within 3 months prior to screening;</li> <li>16. Positive serology for hepatitis B virus (HBV), hepatitis C virus(HCV), or human immunodeficiency virus (HIV);</li> <li>17. 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;</li> <li>18. Abnormal clinical laboratory values as listed below, and determined to be clinically significant by the investigator at the screening:             <ul style="list-style-type: none"> <li>- Serum antinuclear antibody (ANA) &gt;1:80</li> <li>- Rheumatoid factor (RF) result is <math>\geq</math>17 IU/mL</li> <li>- Platelets &lt;150,000 or &gt;500,000/mm<sup>3</sup></li> <li>- White blood cells (WBC) &lt;3,000 or &gt;10,500/mm<sup>3</sup></li> <li>- Absolute neutrophil count (ANC) &lt;1,500/mm<sup>3</sup></li> <li>- Prothrombin time (PT) &lt;9 or &gt;13 seconds</li> <li>- Activated partial thromboplastin time (aPTT) &lt;26.9 or &gt;36.3 seconds</li> <li>- Serum creatinine &gt;2 mg/dL</li> <li>- Glycosylated hemoglobin (HbA1c) &gt;8.5%</li> <li>- Erythrocyte sedimentation rate (ESR) <math>\geq</math>age-adjusted upper limit of reference range (ULRR), i.e. over 50 years old: male <math>\geq</math>20 mm/hr, female <math>\geq</math>30 mm/hr; over 85 years old: male <math>\geq</math>30 mm/hr, female <math>\geq</math>42 mm/hr</li> <li>- C-reactive protein (CRP) &gt;0.5 mg/dL</li> <li>- Aspartate aminotransferase (AST) &gt;84 U/L</li> <li>- Alanine aminotransferase (ALT) &gt;80 U/L</li> </ul> </li> </ol>
--	---

<p><b>INVESTIGATIONAL PRODUCT(S)</b></p>	<p>The UB-311 (UBITh<sup>®</sup> AD Immunotherapeutic Vaccine) is supplied as a single-dose vial containing 300 µg in 0.5 mL solution.</p>
<p><b>PRIMARY ENDPOINT(S) AND MAIN SECONDARY ENDPOINT(S)</b></p>	<p><b>Primary endpoints:</b></p> <ul style="list-style-type: none"> <li>• Safety and tolerability: the safety evaluations include physical examination, vital signs, Amyloid-related Imaging Abnormalities (ARIA), clinical chemistry &amp; hematology tests, and incidence of adverse event (AE)/serious adverse event (SAE); and</li> <li>• The immunogenicity of UB-311 as measured by change from baseline in anti-Aβ antibody levels through the end of the study and response rate.</li> </ul> <p><b>Secondary endpoints:</b></p> <ul style="list-style-type: none"> <li>• The change from baseline in cognitive, functional, and global assessments through the end of the study, including: <ul style="list-style-type: none"> <li>– Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)</li> <li>– Mini-Mental State Exam (MMSE)</li> <li>– Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)</li> <li>– Clinical Dementia Rating-Sum of Boxes (CDR-SB)</li> <li>– Neuropsychiatric Inventory (NPI)</li> </ul> </li> <li>• The change of amyloid burden from baseline to Weeks 52 and 78 in retention of 18F-AV-45, determined by mean standard uptake value ratio (SUVr) of selected regions of interests (ROIs), such as frontal, temporal, parietal, occipital, and precuneus.</li> </ul>
<p><b>STATISTICAL CONSIDERATIONS</b></p>	<p>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:</p> $100\% \times (A+B_1+C+D) / (A+B_1+B_2+C+D)$ <p>where</p> <p>A: number of administered doses of completers</p> <p>B<sub>1</sub>: number of administered doses of subject(s) who drops out due to drug-related AE(s)</p> <p>B<sub>2</sub>: number of missed doses of subject(s) who drops out due to drug-related AE(s)</p> <p>C: number of administered doses of subject(s) who drops out due to drug-unrelated AE(s)</p> <p>D: number of administered doses of subject(s) who drops out not due to AE(s)</p>

	<p><b>Analysis Population</b></p> <p><u>Modified intent-to-treat (mITT) population:</u> 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.</p> <p><u>Per-protocol (PP) population:</u> subjects who receive all planned doses of the study drug, complete the treatment period, fulfil all entry criteria, and have no key protocol deviation.</p> <p><u>Safety population:</u> subjects exposed to at least one dose of the study drug.</p> <p>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.</p> <p>For the analyses of immunogenicity, UB-311 response rate will be calculated for each arm. The change in antibody level will also be compared by a repeated-measures mixed-effects model.</p> <p>For the analyses of efficacy, continuous variables with repeated measures will be analyzed using a mixed-effects model.</p>
<p><b>DURATION OF STUDY PERIOD</b></p>	<p>Screening period: ≤6 weeks</p> <p>Treatment period: 60 weeks</p> <p>Follow-up period: 18 weeks</p>

## 1 INTRODUCTION AND RATIONALE

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disease set to become the largest socioeconomic burden of the developed world over the coming decades<sup>1</sup>. 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%<sup>2-6</sup> and an incidence rate of about 0.54%<sup>7</sup>.

The pathology of AD is characterized by a progressive loss of neurons and synapses with the presence of large numbers of extracellular amyloid plaques and intracellular neurofibrillary tangles. Although symptomatic therapies are available, there is still no proven treatment that can address a variety of neurobehavioral disturbances and reverse progression of AD<sup>1</sup>. Increased amyloid beta (A $\beta$ ) production or reduced A $\beta$  catabolism has been implicated in the pathogenesis of AD. Therapeutic targets have focused on reducing A $\beta$  deposition in brain and evidence shows that antibodies targeting A $\beta$  can improve symptoms of AD. Results from successful immunotherapy with aggregated A $\beta_{1-42}$  in transgenic mice overexpressing A $\beta_{1-42}$  peptide led to the development of the first human active immunization trial with synthetic aggregated A $\beta_{1-42}$  peptide AN1792 in combination with QS-21 adjuvant<sup>1,8</sup>. Analysis of AN1792-treated subjects showed that about 20% developed robust antibody response but available data on efficacy showed no significant effects on exploratory measures of cognition (Alzheimer's Disease Assessment Scale – Cognitive subscale [ADAS-Cog]) or disability (Disability Assessment for Dementia [DAD], Clinical Dementia Rating [CDR], Mini Mental State Examination [MMSE])<sup>1</sup>. However, significant improvements were observed in a nine component neuropsychological test battery (NTB), indicating less worsening of performance in anti-A $\beta$  antibody responders. Improvements in memory were associated with increased antibody response and decreased tau in the cerebrospinal fluid in a small subset of patients. The AN1792-treated subjects were examined by magnetic resonance imaging (MRI) for cerebral volume changes; greater decrease of brain volume was noted without cognitive decline in antibody responders. Postmortem observations from three patients showed brain regions that were devoid of amyloid plaques. Unfortunately, the trial was halted after reports of acute meningoencephalitis in 18 of 300 patients treated with AN1792<sup>1,8,9</sup>.

However, antibodies did not appear to be the cause of meningoencephalitis since adverse reactions had no correlation with the generation of antibodies against A $\beta$ <sup>1</sup>. Examination of two encephalitis cases postmortem revealed a marked CD4 positive T-cell infiltration suggesting that adverse reaction to A $\beta$  immunotherapy was not due to humoral antibody response but due to T-cell mediated response to AN1792. Given that T-cell epitopes have been mapped to the carboxyl terminal domain of A $\beta_{17-42}$ , it was suggested that immunotherapy specifically targeting the active amino peptide terminal epitopes of A $\beta$  and devoid of the carboxyl terminal domain may possibly reduce risk of T-cell mediated inflammatory response<sup>1,10</sup>.

UBITh<sup>®</sup> AD Immunotherapeutic Vaccine (UB-311) is a mixture of two synthetic peptides that include one of two active UBITh<sup>®</sup> helper T-cell epitopes linked to a B-cell epitope from the first 14 amino acids (A $\beta_{1-14}$ ) of the amino terminal domain of A $\beta$  with no epitope spreading to the carboxyl region in A $\beta_{1-42}$ <sup>11,12</sup>. UBITh<sup>®</sup> T-cell epitopes are derived from virus T-helper cell peptide epitopes rather than from A $\beta$  peptide and thus the T helper cells activated by UB-311 are not likely to cross-react with A $\beta$ <sup>11,12</sup>. The designated UBITh<sup>®</sup> T-cell epitopes are promiscuous and highly potent and expected to provide a broader and stronger T-cell help than the T helper sites intrinsic to A $\beta$ . UB-311 is formulated with mineral salts that have been licensed to be used as an adjuvant by U.S.

FDA. The T-cell response typically associated with this adjuvant is Th-2 response as evidenced by the stimulation of IL-4 cytokine secretion in mouse studies<sup>13,14</sup>.

Specificity of UB-311 to amino terminal A $\beta$ <sub>1-14</sub> reduces the likelihood of a T-cell mediated inflammatory response as shown from the results of the preclinical studies in guinea pigs, baboons and macaques. Baboons aged more than 10 years immunized with UB-311 at Weeks 0, 3 and 6 and boosted at Weeks 78, 81 and 104 had no adverse reactions on observation. The treated baboons demonstrated high antibody titers with specificity to the A $\beta$ <sub>1-14</sub> domain, but not to the carboxyl domain at all dose levels. No unexpected adverse reactions at the injection site have been noted in any of the safety and immunogenicity studies conducted in guinea pigs and baboons. An acute and chronic toxicity study in Cynomolgous macaques demonstrated safety, tolerability and immunogenicity of UB-311.

The dose selected for UB-311 is based on the data obtained from preclinical studies (Table 1). The anti-A $\beta$  antibodies were detected in sera of four of six Macaques after one immunization at the 150  $\mu$ g/dose level at 3 weeks post injection and six of six Macaques at the 750  $\mu$ g/dose level at 3 weeks post injection. The immunogenicity was also detected in sera of five of six baboons at the 300  $\mu$ g/dose level at 3 weeks post injection, and two of two baboons at the 1200  $\mu$ g/dose level at 3 weeks post injection. Therefore, the 300  $\mu$ g/dose was considered as an appropriate dose and the doses over 750  $\mu$ g were at the plateau of the optimal dose. Regarding the safety, no obvious adverse events occurred in the macaque groups receiving either 150 or 750  $\mu$ g/dose; only some site reactogenicity occurred in the group receiving the higher dose, 750  $\mu$ g/dose. Since human body weights are 10-fold to 20-fold higher than that of macaques, the safety associated with these doses will not be of concern. The 300  $\mu$ g/dose was selected as the dose for further clinical evaluation because it was found to be safe, well tolerated and strongly immunogenic as shown by all available preclinical evidences. In the Phase I clinical trial, UB-311 has demonstrated satisfying safety and tolerability profiles when administered to patients with clinically documented mild to moderate Alzheimer's disease (AD). It is also capable of eliciting antibodies with specificity to the N-terminus of the A $\beta$ <sub>1-14</sub> domain after administration by intramuscular route without causing any serious adverse events (SAEs) or intolerable adverse events (AEs). The response rate is 100%, using greater than one-sided 95% upper limit of the mean baseline titer as cutoff.

**Table 1.**

Species [BW]	Peptide dose ( $\mu$ g)		CpG ODN dose ( $\mu$ g) <sup>†</sup>		Antibody titer Log <sub>10</sub> >2 <sup>‡</sup>	
	per animal	per kg BW	per animal	per kg BW <sup>§</sup>	3 weeks post 1 dose <sup>†</sup>	3 weeks post 2 doses <sup>†</sup>
Guinea pig [300 – 400 g]	1	2.5 – 3.3	0.2	0.5 – 0.7	0 / 3	0 / 3
	3	7.5 – 10	0.6	1.5 – 2.0	0 / 3	0 / 3
	10	25 – 33	2.0	5.0 – 6.7	0 / 6	5 / 6
	30	75 – 100	6	15 – 20	1 / 6	6 / 6
	100	250 – 333	20	50 – 67	2 / 3	3 / 3
	300	750 – 1000	60	150 – 200	2 / 3	3 / 3
Macaque [4 – 5 kg]	150	30 – 37.5	60	12 – 15	4 / 6	6 / 6
	750	150 – 187.5	150	30 – 37.5	6 / 6	6 / 6
Baboon	300 – A <sup>¶</sup>	20 – 30	60	4 – 6	3 / 4	4 / 4

[10 – 15 kg]	300 – B <sup>‡</sup>	20 – 30	60	4 – 6	2 / 2	2 / 2
	1200	80 – 120	240	16 – 24	2 / 2	2 / 2

† For a 600 µg/mL peptide dosage, CpG ODN dosage is 120 µg/mL and aluminum content is 1600 µg/mL.

‡ Log<sub>10</sub> values >2 are scored as positive anti-Aβ titers.

§ For use in humans, the concentration of the peptide:CpG ODN immunostimulatory complex is 300 µg peptide to 60 µg CpG ODN delivered in 0.5 mL Adjuphos by intramuscular route.

¥ Baboons immunized in Part A at 0 and 3 weeks and in Part B at 78 and 81 weeks (after 72 weeks rest period).

BW=body weight; NA=not available.

The definitive diagnosis of AD requires the presence of progressive dementia and the histopathological evidence from a biopsy or autopsy, i.e. neuritic plaques composed of Aβ aggregates and neurofibrillary tangles formed from phosphorylated tau protein<sup>15,16</sup>. The invention of Aβ imaging agent facilitates early evaluation of AD neuropathology and serves as a potential biomarker for clinical trials of disease-modifying therapies in AD. The <sup>11</sup>C-labeled Pittsburgh compound B (<sup>11</sup>C-PiB) was the first positron emission tomography (PET) imaging agent to visualize Aβ plaques in living patients<sup>17,18</sup>. Rinne and colleagues have successfully demonstrated changes in Aβ load in AD patients treated with bapineuzumab, a passive immunotherapy targeting the N terminus of Aβ, by <sup>11</sup>C-PiB PET<sup>19</sup>. However, its utilization is limited by a short half-life of 20 minutes. Florbetapir F18 (also known as 18F-AV-45, Avid Radiopharmaceuticals, Inc. and Eli Lilly and Company), a radioactive diagnostic agent tagged with a radioisotope, fluorine-18, was recently approved by U.S. FDA with satisfying safety and effectiveness profiles, and a preferable half-life of 110 minutes as compared to <sup>11</sup>C-PiB<sup>20</sup>. In this Phase IIa trial, the change of Aβ burden in brain as a proof-of-concept for the mechanism of UB-311 will be evaluated by using 18F-AV-45 PET imaging.

A follow-up report on a Phase I study showed that immunization with AN1792 could completely remove amyloid plaques as demonstrated by postmortem assessment, but patients still had the symptoms of end-stage dementia before death<sup>21</sup>. This finding suggests that clearance of amyloid plaques alone cannot repair existing damaged neurons and prevent disease progression. Increasing evidence from patients with mild-to-moderate AD has shown that the disease might be already beyond the disease-modifying effect of an immunotherapy<sup>22</sup>. Thus it would be reasonable to initiate treatment with disease-modifying effect before substantial neuronal loss or neuropathologic change that has damaged the brain. In the Phase I clinical trial with UB-311, a subset of older patients (age ≥60 years) with higher baseline MMSE scores (MMSE ≥20) showed both high antibody responses to the UB-311 vaccine after 3 dosages and improved clinical profiles as assessed by ADAS-Cog, MMSE and ADCS-CGIC scores<sup>23</sup>. Thus, subjects with mild AD are selected as the target patient population in this Phase IIa study to further demonstrate the safety and tolerability, establish the efficacy profiles, and explore other clinical benefits of UB-311. The Phase IIa clinical study will evaluate UB-311 as a promising candidate for active immunotherapy of mild Alzheimer’s disease.

## 2 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-A $\beta$  antibodies.

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 18F-AV-45 PET imaging.

## 3 TRIAL DESIGN

This is a 78-week, randomized, double-blind, placebo-controlled, three-arm parallel-group, multicenter Phase IIa trial.

Individuals who were enrolled in the Phase I trial will be excluded from the Phase IIa trial.

### 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 first and second stage screenings,
- A 60-week double-blind randomized treatment period, which includes 2 different UB-311 dosing regimen arms and 1 placebo arm, and
- An 18-week follow-up period.

**Table 3.1 Clinical Schematic Diagram**

	Screening		Treatment											Follow-up	
Visit	S1	S2	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Week	-6	~ 0	0	4	12	16	24	28	36	40	48	52	60	64	78
Treatment arms															
<b>Arm 1</b>			↑	↑	↑		↑		↑		↑		↑		
<b>Arm 2</b>			↑	↑	↑		↑p		↑		↑p		↑		
<b>Arm 3</b>			↑p	↑p	↑p		↑p		↑p		↑p		↑p		

↑ : UB-311    ↑ p: placebo

#### 3.1.1 Screening Period

Subjects with probable Alzheimer’s disease based on National Institute of Neurological and Communicative Disorders and Stroke, and Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) Criteria and National Institute on Aging–Alzheimer’s Association (NIA-AA) guidelines are screened at the first stage screening (S1, Weeks -6~0). All laboratory tests required



for evaluating the eligibility of the subjects are performed at S1.

Subjects meeting inclusion criteria 1 to 14 and none of the exclusion criteria are eligible for the second stage screening (S2, Weeks -6~<0) for the positive of  $\beta$  amyloid ( $A\beta$ ) plaques on 18F-AV-45 PET by an imaging expert per central independent review (See Section 3 of Appendix 1 Imaging Protocol).

### 3.1.2 Treatment Period

Subjects meeting all inclusion criteria, presenting no exclusion criteria, and with  $A\beta$  imaging in the brain enter the treatment period, from V1 (Week 0) to V11 (Week 60). These subjects are randomized into one of the 3 treatment arms before treatment initiation at V1.

### 3.1.3 Follow-up Period

The follow-up period comprises 2 visits: V12 (Week 64) and V13 (Week 78).

## 3.2 Endpoints

### 3.2.1 Primary

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- $A\beta$  antibody levels through the end of the study
  - Response rate (see section 6.1.2 for definition)

### 3.2.2 Secondary

The secondary endpoints are:

- The change from baseline in cognitive, functional, and global assessments through the end of the 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 of amyloid burden from baseline to Weeks 52 and 78 in retention of 18F-AV-45, determined by mean standard uptake value ratio (SUVR) of selected regions of interests (ROIs), such as frontal, temporal, parietal, occipital, and precuneus.

### **3.3 Description of Blinding Methods**

The UB-311 and placebo vials are indistinguishable by appearance. Each treatment box is labeled with a number, which is generated by a computer program from UNS's delegate CRO. Investigators do not have access to the randomization code except under circumstances described in section 6.4.

To maintain the blind during the trial, neither the investigator nor the sponsor will have access to the data that could potentially compromise study blindness during the study.

### **3.4 Description of Randomization**

The list of randomized numbers of treatment kits is generated centrally by UNS's delegate CRO. UB-311 and/or placebo are packaged in accordance with this list.

UNS's delegate CRO provides a list of the randomized treatment box number and a randomization scheme to the Interactive Voice or Web Response System (IVRS/IWRS). The IVRS/IWRS generates the subject randomization list to allocate the treatments to subjects.

Subjects are randomized to one of the three arms in 1:1:1 ratio, providing a projected equal distribution of subjects among groups.

### **3.5 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 committees of the Data and Safety Monitoring Board (DSMB), 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

It is planned to recruit approximately 45 subjects (15 per arm) to receive study treatment in the 78-week double-blind, placebo-controlled study. The randomization procedure continues until the target number of treated patients is reached.

The screen failure rate is estimated to be 50%; therefore, to reach this number it is planned to screen at least 90 subjects.

### 4.2 Inclusion Criteria

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

1. Male or female aged between 60-90 years old.
2. Probable Alzheimer's disease based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines.
3. Mini-Mental State Examination (MMSE) scores between 20 and 26 (inclusive).
4. Clinical dementia rating (CDR) scores of 0.5 or 1.
5. At least 6 years of education or sufficient work history (to exclude mental retardation).
6. Visual and auditory acuity adequate for neuropsychological testing.
7. 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.
8. Hachinski ischemic score (HIS)  $\leq 4$  (original score).
9. Geriatric Depression Scale-Short Form (GDS-SF)  $< 6$ .
10. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
11. 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.
12. 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), to perform study-related AD scales and to accompany or delegate a companion with the subject to all visits. A companion needs not to be a family member (with kinship).
13. Both patient and his/her caregiver should sign the written informed consent before undergoing any study procedures.
14. Agree not to donate blood or blood products for transfusion during the study and for 3 months thereafter.

15. A positive of A $\beta$  plaque on 18F-AV-45 PET by an imaging expert (confirmed during the second stage of screening per central independent review).

### **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 deficits or known structural brain abnormalities.
2. Screening MRI scan with evidence of central nervous system (CNS) infection, cerebrovascular disease, infarction, or other focal lesions, or a single area of superficial siderosis, or a prior macrohemorrhage, or more than four microhemorrhages, multiple lacunes or lacunes in a critical memory structure.
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. Current participation in clinical studies involving ADAS-Cog, MMSE, ADCS-ADL, CDR-SB, or NPI being collected more than one time per score per year.
13. Previous exposure to any anti-A $\beta$  immunotherapy.
14. 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).
15. Received blood or blood derivatives treatment within 3 months prior to screening.

16. Positive serology for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
17. 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.
18. Abnormal clinical laboratory values as listed below, and determined to be clinically significant by the investigator at the screening:
  - Serum antinuclear antibody (ANA) >1:80
  - Rheumatoid factor (RF) result is  $\geq 17$  IU/mL
  - Platelets <150,000 or >500,000/mm<sup>3</sup>
  - White blood cells (WBC) <3,000 or >10,500/mm<sup>3</sup>
  - Absolute neutrophil count (ANC) <1,500/mm<sup>3</sup>
  - Prothrombin time (PT) <9 or >13 seconds
  - Activated partial thromboplastin time (aPTT) <26.9 or >36.3 seconds
  - Serum creatinine >2 mg/dL
  - Glycosylated hemoglobin (HbA1c) >8.5%
  - Erythrocyte sedimentation rate (ESR)  $\geq$  age-adjusted upper limit of reference range (ULRR), i.e. over 50 years old: male  $\geq 20$  mm/hr, female  $\geq 30$  mm/hr; over 85 years old: male  $\geq 30$  mm/hr, female  $\geq 42$  mm/hr
  - C-reactive protein (CRP) >0.5 mg/dL
  - Aspartate aminotransferase (AST) >84 U/L
  - Alanine aminotransferase (ALT) >80 U/L

#### **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 13/ET (see sections 8.2 and 8.3) should be completed at the early termination visit when applicable, including: ECG, physical examination, vital signs, clinical chemistry and hematology tests, serum anti-A $\beta$  antibody level evaluation, recordation of any AE/SAE, concomitant treatments (medications/therapy), imaging evaluations (18F-AV-45 PET and MRI), and neuropsychological tests (including MMSE, CDR-SB, ADAS-Cog, ADCS-ADL, and NPI). 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 78), 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<sup>®</sup> AD Immunotherapeutic Vaccine), 300 µg per 0.5 mL per vial.

Placebo: delivery vehicle without UB-311 active peptides and CpG.

### 5.2 Dosing Regimens and Rationale

Eligible subjects are randomly assigned in 1:1:1 ratio to one of the following treatments:

- Arm 1: UB-311 for a total of 7 intramuscular (IM) injections at Weeks 0, 4, 12, 24, 36, 48, and 60.
- Arm 2: UB-311 for a total of 5 IM injections at Weeks 0, 4, 12, 36, and 60. In order to maintain the blindness, subjects assigned to arm 2 will receive 2 IM injections of placebo at Weeks 24 and 48.
- Arm 3: placebo for a total of 7 IM injections at Weeks 0, 4, 12, 24, 36, 48, and 60.

Injections will be given on alternate arms or at different sites, which will be recorded.

The 300 µg of UB-311 in 0.5 mL sterile aqueous solution is the maximal concentration feasible in the current intramuscular injection formulation containing CpG-ODN and Adjuvphos. Therefore, the dose escalation in the Phase IIa study will be based on the cumulative doses according to various treatment schedules instead of different amount of UB-311 per injection.

A total of three injections of UB-311 at Weeks 0, 4, and 12 with a cumulative dose of 900 µg were evaluated in the Phase I clinical trial that showed acceptable safety, tolerability, immunogenicity, and positive clinical outcome in mild to moderate AD patients over a one-year period. In the Phase IIa study, the dose will be escalated based on increased number of injections than the Phase I study. Subjects assigned to Arm 1 will receive 7 injections of UB-311, 300 µg each at Weeks 0, 4, 12, 24, 36, 48, and 60 with a cumulative dose of 2,100 µg. Subjects assigned to Arm 2 will receive 5 injections of UB-311, 300 µg each at Weeks 0, 4, 12, 36, and 60 with a cumulative dose of 1,500 µg.

The Phase I study showed that three priming doses at Weeks 0, 4, and 12 successfully established sufficient immunogenicity against Aβ, thus the priming schedule was adopted for the current study. Additional doses for Arm 1 and Arm 2 at the frequency of 3 and 6 months, respectively, are intended to assess the requirement for maintaining elicited antibody levels. Furthermore, the dosing regimen of Arm 1 represents the most frequent injection schedule, allowing evaluation of safety and efficacy of the strongest antibody response.

### 5.3 Handling of Study Drug

#### 5.3.1 Packing and Labelling

The treatment box for each subject includes 7 vials numbered in the order of injection. The boxes for Arm 1 contain 7 vials of UB-311. The boxes for Arm 2 contain 5 vials of UB-311 and 2 vials of placebo. The boxes for Arm 3 contain 7 vials of placebo. Each box and vial is labelled with the randomization code, storage condition, and manufacturer.

### 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 (e.g. antihypertensives).

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 and during the study period.
- Ginkgo biloba
- Piracetam (Nootropil)
- Vitamin E ( $\leq 400$  IU/day)

### 5.5.2 Prohibited Medicines



The following medications are prohibited within 4 weeks prior to the first screening visit (S1) and during the study period:

- Antiparkinson's drugs (e.g. L-dopa, dopamine agonists, amantadine)
- Neuroleptics, with the exception of haloperidol  $\leq 2$  mg/day, quetiapine  $\leq 300$  mg/day, risperidone  $\leq 2$  mg/day, sulpiride  $\leq 200$  mg/day, and olanzapine  $\leq 10$  mg/day
- Sedative/hypnotics (in exceptional cases where short-acting and intermediate-acting benzodiazepines are conditionally allowed, for example, midazolam in oral dosage  $\leq 7.5$  mg/day for sleep only, midazolam injection  $\leq 5$  mg/day for office procedures with sedation only, oxazolam  $\leq 10$  mg/day, alprazolam  $\leq 1$  mg/day, lorazepam  $\leq 1$  mg/day, bromazepam  $\leq 12$  mg/day with maximum starting dose of 1.5 mg, twice a day, estazolam  $\leq 1$  mg/day at bedtime for sleep only, and other hypnotics such as zolpidem  $\leq 10$  mg/day, and zopiclone  $\leq 7.5$  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 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 from baseline in anti-A $\beta$  antibody levels through the end of the study (Week 78)
- Response rate (see section 6.1.2 for definition)

#### 6.1.1 Anti-A $\beta$ antibody measurement

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

The level of anti-A $\beta$  antibodies is assessed at every visit throughout the study period from V1 to V13 (Weeks 0/baseline, 4, 12, 16, 24, 28, 36, 40, 48, 52, 60, 64, and 78). For visits that UB-311 or placebo is scheduled to be administrated (V1, V2, V3, V5, V7, V9, and V11), 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 9.2.2 for definition) at any visit after baseline. Response rate will be calculated as the percent of the number of antibody responders versus the total number of subjects for each arm.

### 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 endpoints in this study.

#### 6.3.1 Evaluation variables

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

- Cognition: ADAS-Cog and MMSE
- Function: ADCS-ADL

- Global: CDR-SB
- Behavior: NPI

### 6.3.1.2 The change of amyloid burden from baseline to Week 52 and Week 78 in retention of 18F-AV-45

The data will be expressed by mean regional standard uptake value ratio (SUVR).

## 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 and CDR/CDR-SB are evaluated at the first screening (S1), and at Weeks 24 (V5), 48 (V9) and 78 (V13). ADAS-Cog, ADCS-ADL, and NPI are evaluated at baseline (V1), and at Weeks 28 (V6), 52 (V10) and 78 (V13).

### 6.3.2.2 18F-AV-45 retention measurement

18F-AV-45 PET is conducted at the second screening (S2), and at Weeks 52 (V10) and 78 (V13) to assess the change in A $\beta$  burden from baseline to Weeks 52 and 78 (see Section 3 of Appendix 1 Imaging Protocol).

In case of scanning failure, re-injection/re-scanning of 18F-AV-45 is allowed. The detailed procedures of 18F-AV-45 PET are described in a separate manual, 18F-AV-45 PET Imaging Manual.

## 6.4 Measures to protect blinding of this trial

This is a double-blind study. In order to protect blinding, study drug will be labelled with individual unique randomization codes. 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 call IVRS/IWRS 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.

The treatment arm for each subject will be coded so that the subject, investigator, and research staff do not know the arm assignment until the end of the study. Personnel related to analysis, statistics, and report writing will remain blinded before database lock.

## 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 0 (V1/baseline), 4 (V2), 12 (V3), 24 (V5), 36 (V7) 48 (V9), and 60 (V11). 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 (S1 and S2) and at every visit throughout the study (V1 to V13). Neurology examination and vital signs will be assessed again 30-60 minutes after study drug injection at Weeks 0 (V1/baseline), 4 (V2), 12 (V3), 24 (V5), 36 (V7), 48 (V9), and 60 (V11).

#### 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 the first screening (S1) and at Weeks 52 (V10) and 78 (V13). 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 the first screening (S1) and at Weeks 12 (V3), 24 (V5), 36 (V7), 48 (V9), 60 (V11), and 78 (V13) to monitor ARIA and age-related white matter changes (ARWMC) that may be induced by amyloid-modifying therapy. Please refer to Appendix 1 Imaging Protocol for the detailed methods.

#### 7.1.6 Safety laboratory

The following laboratory data are collected:

- Hematology: complete blood count including differential cell count and absolute neutrophil count at the first screening (S1) and every visit throughout the study (V1 to V13).
- Clinical chemistry: HbA1c at the first screening (S1); glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin at the first screening (S1) and every visit throughout the study (V1 to V13).
- Inflammatory parameters: RF and ANA at the first screening (S1); CRP and ESR at the first screening (S1), and at Weeks 4 (V2), 16 (V4), 28 (V6), 40 (V8), 52 (V10), and 64 (V12); TNF- $\alpha$ , IL-6, and IL-8 at Weeks 0 (V1), 4 (V2), and 64 (V12).

For visits that UB-311 or placebo is scheduled to be administered (V1, V2, V3, V5, V7, V9, and V11), 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 A $\beta$  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:

<b>Severity of AE</b>	<b>Description</b>
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:

<b>Relationship</b>	<b>Description</b>
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).

### **7.9 Data and Safety Monitoring Board**

A Data and Safety Monitoring Board (DSMB) with members independent from the sponsor and the clinical investigators is implemented in order to ensure the protection and safety of enrolled patients in the study. The DSMB members include:

- An expert in the clinical aspects of the Alzheimer’s disease patient population being studied,
- A biostatistician, and
- An investigator with expertise in current clinical trials conduct and methodology.

Each DSMB member will sign a Conflict of Interest Statement at the time they are invited to participate to declare that he/she does not have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB.

The DSMB is responsible for reviewing safety data, study conduct, and progress. Based on the review, the DSMB makes recommendations to the clinical investigators concerning the continuation, modification, or termination of the trial. In the V203-AD trial, the DSMB will convene for the first time after the 9<sup>th</sup> subject completes Visit 6, for the second time after the 18<sup>th</sup> subject completes Visit 10, and for the third time after the 27<sup>th</sup> subject completes V13 to assess the safety data in the V203-AD trial. An emergency meeting of the DSMB may be called at any time by the DSMB Chair should questions on participants’ safety or other unanticipated problems arise.

It is the responsibility of CRO or sponsor to ensure that the DSMB is informed about safety information relevant to the study. This includes providing the DSMB with preclinical data, results from the phase I study, and the phase IIa protocol before initiation of the trial, and a DSMB report at least one week prior to a scheduled meeting. The CRO is responsible for preparing the DSMB briefing materials, which consist of:

- Subject recruitment, retention, and withdrawal information
- AEs and SAEs
  - Tabulated by preferred term, intensity, seriousness, duration, treatment given, and the relationship to the study drug and study procedure
  - Individual events of particular concern
- Tabulated clinical test results and laboratory values (e.g. raw values, changes/shifts from baseline, and clinical abnormalities), including clinical chemistry, hematology tests, and 12-lead electrocardiogram (ECG)
- Vital signs and physical exam outcomes
- 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.

Any other safety-related data requested by the DSMB

At the conclusion of a DSMB meeting, the DSMB will issue a summary report, which documents the review of data and outcomes across all sites took place on a given date. It should summarize the DSMB members' opinions on the cumulative data reported from all participating sites without disclosure by treatment arm. It should also inform clinical investigators of the DSMB members' conclusions with respect to progress or need for modification of the protocol. The summary report will be forwarded to each clinical investigator and the sponsor. The clinical investigator is required to transmit the summary report to his/her local IRB.

## **7.10 Risk Management**

Postvaccination meningoencephalitis was reported in over 6% of patients treated with AN1792 for AD<sup>9,10</sup>. Based on the experiences of AN1792 clinical trials, the following measures are used to manage potential risks:

### **1. Strict Enrollment Criteria**

Subjects with any evidence of CNS infection, infarction, other focal lesions, more than four microhemorrhages, multiple lacunes or lacunes in a critical memory structure by MRI, as well as having history of autoimmune disease will be excluded from the study.

### **2. Sample Size**

A total of 45 subjects are planned to be enrolled. Among them, 30 subjects receiving UB-311 are anticipated to be able to detect an adverse event with an incidence of 4%.

### **3. Regular MRI evaluations**

Brain MRI scans will be performed every 12 weeks during the treatment period and also at the end of study to ensure that any change or lesion in the brain, such as meningoencephalitis, vasogenic edema or microhemorrhage can be detected as early as possible.

### **4. Regular Clinical Monitoring**

Clinical symptoms and laboratory data of hematology and clinical chemistry will be monitored closely throughout the study. Adverse events will be followed until conditions are resolved or stabilized.

### **5. Establishment of DSMB**

DSMB will be implemented in this trial and DSMB meetings will be held as scheduled to ensure the protection and safety of enrolled subjects. DSMB meeting will also be held in response to any urgent safety events.

### **6. Meningoencephalitis Management by Investigator**

If meningoencephalitis occurs, investigator will treat the subject with standard clinical procedures, such as giving bed rest, avoiding daylight, supplying fluid, and providing medications for pain control including anti-inflammatory, anti-convulsant and anti-emetic drugs. Corticosteroids may be prescribed to reduce tissue swelling or cerebral edema if necessary.

## 8 STUDY PROCEDURES

### 8.1 Study Visits

The study consists of a screening period (up to 6 weeks) with 2 visits, a double-blind, placebo-controlled treatment period (60 weeks) with 11 visits, and a double-blind follow-up period (18 weeks) with 2 visits. From V2 (Week 4) to V12 (Week 64), a time frame of  $\pm 3$  days is acceptable using the day of V1 as reference (Day 0), i.e. if one visit date is changed, the next visit should take place according to the original schedule. For V13 (Week 78), a time frame of  $\pm 7$  days is acceptable using the day of V1 as reference. Out of visit/dosing window and missing visit/dose are considered as protocol deviations. Additional items for research purposes at each visit will be described in details in a separate research protocol (Appendix 2).

#### 8.1.1 The First Stage Screening ( $-42 \leq \text{Day} < 0$ )

The first screening (S1) may take place no more than 42 days prior to randomization. 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 informed 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 except for 18F-AV-45 PET imaging
- Demographics (age, gender, race, years of education)
- Complete medical history and concomitant diseases
- Concomitant and previous medication (within the last 3 months)
- Physical examination and height
- Vital signs, including temperature, respiratory rate, heart rate, blood pressure, and body weight
- Structural MRI scanning
- 12-lead ECG
- Survey instruments
  - NINCDS-ADRDA
  - HIS score
  - MMSE
  - CDR / CDR-SB

- 
- ECOG
  - GDS-SF
  - Record of adverse event (AE) and serious adverse event (SAE)
  - Blood collection for testing of:
    - HIV, HCV, and HBsAg
    - RF, ANA, CRP, ESR, PT, and aPTT
    - Serum pregnancy test (only for females with childbearing potential)
    - 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)

#### 8.1.2 The Second Stage Screening (-42 ≤ Day < 0)

This visit is scheduled between the first stage screening visit and visit 1 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
- 18F-AV-45 PET imaging

#### 8.1.3 Visit 1 (Week 0, Day 0 / baseline)

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

- Verification of Inclusion/Exclusion criteria and check for eligibility
- IVRS/IWRS call for randomization
- Survey instruments
  - ADAS-Cog
  - ADCS-ADL
  - NPI
- 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-A $\beta$  antibodies
- TNF- $\alpha$ , 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)
- APO-E genotyping
- 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 2 (Week 4, Day 28)

This visit (V2) should be scheduled 4 weeks  $\pm$  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-A $\beta$  antibodies
  - CRP, ESR, TNF- $\alpha$ , 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 assessment, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

#### 8.1.5 Visit 3 (Week 12, Day 84)

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

- Structural MRI scanning (should be scheduled < 7 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-A $\beta$  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)
- Injecting study drug
- Injection site assessment, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

#### 8.1.6 Visit 4 (Week 16, Day 112)

This visit (V4) should be scheduled 16 weeks  $\pm$  3 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
- Blood collection for:
  - Anti-A $\beta$  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)

#### 8.1.7 Visit 5 (Week 24, Day 168)

This visit (V5) should be scheduled 24 weeks  $\pm$  3 days after V1 and includes:

- Structural MRI scanning (should be scheduled < 7 days before the injection of study drug)
- Survey instruments
  - MMSE
  - CDR-SB
- 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-A $\beta$  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)
- Injecting study drug
- Injection site assessment, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

#### 8.1.8 Visit 6 (Week 28, Day 196)

This visit (V6) should be scheduled 28 weeks  $\pm$  3 days after V1 and includes:

- Survey instruments
  - ADAS-Cog
  - ADCS-ADL
  - NPI
- 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-A $\beta$  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)

#### 8.1.9 Visit 7 (Week 36, Day 252)

This visit (V7) should be scheduled 36 weeks  $\pm$  3 days after V1 and includes:

- Structural MRI scanning (should be scheduled < 7 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 sampling for: (before the UB-311/Placebo injection)
  - Anti-A $\beta$  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)
- Injecting study drug
- Injection site assessment, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

#### 8.1.10 Visit 8 (Week 40, Day 280)

This visit (V8) should be scheduled 40 weeks  $\pm$  3 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
- Blood sampling for:
  - Anti-A $\beta$  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)

#### 8.1.11 Visit 9 (Week 48, Day 336)

This visit (V9) should be scheduled 48 weeks  $\pm$  3 days after V1 and includes:

- Structural MRI scanning (should be scheduled < 7 days before the injection of study drug)
- Survey instruments
  - MMSE

- CDR-SB
- 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/Placebo injection)
  - Anti-A $\beta$  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)
- Injecting study drug
- Injection site assessment, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

#### 8.1.12 Visit 10 (Week 52, Day 364)

This visit (V10) should be scheduled 52 weeks  $\pm$  3 days after V1 and includes:

- 18F-AV-45 PET scanning (a time frame of  $\pm$  7 days is acceptable)
- 12-lead ECG
- Survey instruments
  - ADAS-Cog
  - ADCS-ADL
  - NPI
- 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:
  - Anti-A $\beta$  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)

#### 8.1.13 Visit 11 (Week 60, Day 420)

This visit (V11) should be scheduled 60 weeks  $\pm$  3 days after V1 and includes:

- Structural MRI scanning (should be scheduled < 7 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 sampling for: (before the UB-311/Placebo injection)
  - Anti-A $\beta$  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)
- Injecting study drug
- Injection site assessment, vital signs (except body weight), and neurology examination of physical examination 30-60 minutes after injection

#### 8.1.14 Visit 12 (Week 64, Day 448)

This visit (V12) should be scheduled 64 weeks  $\pm$  3 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
- Blood sampling for:
  - Anti-A $\beta$  antibodies
  - CRP, ESR, TNF- $\alpha$ , 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)

### 8.1.15 Visit 13 (Week 78, Day 546)

This visit (V13) should be scheduled 78 weeks  $\pm$  7 days after V1 and includes:

- Structural MRI scanning
- 18F-AV-45 PET scanning
- 12-lead ECG
- Survey instruments
  - MMSE
  - CDR-SB
  - ADAS-Cog
  - ADCS-ADL
  - NPI
- 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:
  - Anti-A $\beta$  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)

## 8.2 Events and Time Schedule

Visit	S1 <sup>9</sup>	S2 <sup>9</sup>	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Week	-6	~ 0	0/BL	4	12	16	24	28	36	40	48	52	60	64	78/ET
Day	-42	~ 0	0	28±3	84±3	112±3	168±3	196±3	252±3	280±3	336±3	364±3	420±3	448±3	546±7
ICF, medical history & concomitant disease, demographics	X														
Incl./excl. criteria	X	X	X												
Randomization			X												
ECG	X											X			X
MRI <sup>1</sup>	X				X		X		X		X		X		X
18F-AV-45 PET <sup>2</sup>		X										X			X
APO-E genotyping			X												
NINCDS-ADRDA, HIS, GDS-SF, ECOG	X														
MMSE, CDR <sup>3</sup> /CDR-SB	X						X				X				X
ADAS-Cog, ADCS-ADL & NPI			X					X				X			X
AE/SAE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and concomitant medicines	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PE <sup>4</sup> /vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV, HCV, HBsAg test	X														
Clinical chemistry <sup>5</sup> & hematology <sup>5</sup>	X		X*	X*	X*	X	X*	X	X*	X	X*	X	X*	X	X
Inflammatory <sup>6</sup>	X		X	X*		X		X		X		X		X	
PT & aPTT	X														
Serum pregnancy test <sup>7</sup>	X														
Anti-Aβ Ab level in serum			X*	X*	X*	X	X*	X	X*	X	X*	X	X*	X	X
Vaccination/injection site assessment/ Neurology/vital signs <sup>8</sup>			X	X	X		X		X		X		X		
vMRI	X										X				X
fMRI	X										X				X
Plasma Aβ <sub>40/42</sub> levels			X*	X*	X*	X	X*	X	X*	X	X*	X	X*	X	X
Anti-Aβ <sub>1-42</sub> monomer & oligomer Antibodies			X*	X*	X*	X	X*	X	X*	X	X*	X	X*	X	X
CSF tau & Aβ <sub>40/42</sub> levels (optional)			X*									X			X

BL=baseline; ET=early termination; vMRI=volumetric magnetic resonance imaging; fMRI=functional magnetic resonance imaging

- For V3 (Week 12), V5 (Week 24), V7 (Week 36), V9 (Week 48), and V11 (Week 60), MRI should be scheduled <7 days before the injection of study drug. For V13, a time frame of ± 7 days is acceptable.
- For V13, a time frame of ± 7 days is acceptable.
- CDR: for S1 only
- Including height (for S1 only)
- 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 V13); Hematology: complete blood count including differential

- cell count and ANC at S1 and every visit throughout the study (V1 to V13).
6. Inflammatory parameters: RF and ANA (for S1 only); CRP and ESR: for S1, V2 (Week 4), V4 (Week 16), V6 (Week 28), V8 (Week 40), V10 (Week 52), and V12 (Week 64); TNF- $\alpha$ , IL-6, and IL-8: for V1, V2 (Week 4), and V12 (Week 64).
  7. For females with childbearing potential.
  8. 30-60 minutes after injection. Vital sign: not need to measure body weight.
  9. Criteria are screened at S1. Subjects meeting inclusion criteria 1 to 14 and none of the exclusion criteria are eligible for the S2. S1 and S2 should be done within 6 weeks before V1.
- \* Blood or CSF specimens should be drawn before the UB-311/Placebo injection.

### 8.3 Blood Sample Collection

For visits that UB-311 or placebo is scheduled to be administrated (V1, V2, V3, V5, V7, V9, and V11), blood samples will be collected before the treatment.

Visit	S1	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
<b>Week</b>	-6~0	0/BL	4	12	16	24	28	36	40	48	52	60	64	78/ET
<b>Day</b>	-42~0	0	28±3	84±3	112±3	168±3	196±3	252±3	280±3	336±3	364±3	420±3	448±3	546±7
<b>Vaccination</b>		X	X	X		X		X		X		X		
<b>Clotted Blood</b>														
HIV, HCV, HBsAg, RF, ANA and serum pregnancy test <sup>1</sup>	5 mL													
Clinical chemistry <sup>2</sup> except HbA1c and Glucose AC, CRP <sup>3</sup>	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL
TNF- $\alpha$ , IL-6, and IL-8		3.5 ml	3.5 ml										3.5 ml	
Anti-A $\beta$ , and anti- A $\beta$ <sub>1-42</sub> monomer and oligomer <sup>4</sup>		2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL
<b>EDTA Blood</b>														
Hematology <sup>5</sup> and HbA1c <sup>6</sup>	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL	3 mL
ESR	3 mL		3 mL		3 mL		3 mL		3 mL		3 mL		3 mL	
APO-E genotyping		3 mL												
A $\beta$ <sub>40/42</sub> <sup>4</sup>		2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL
<b>NaF Blood</b>														
Glucose AC	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml	2 ml
<b>Citrated Blood</b>														
PT, aPTT	2.7 mL													

BL=baseline; ET=early termination

Note: In the case of testing failure, residual samples of the subject from other tests may be used for retesting.

1. Only for females with childbearing potential;
2. Clinical chemistry: AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin at S1 and every visit throughout the study (V1 to V13);
3. CRP: for screening, V2 (Week 4), V4 (Week 16), V6 (Week 28), V8 (Week 40), V10 (Week 52), and V12 (Week 64);
4. For research study;
5. Hematology: complete blood count including differential cell count and ANC at S1 and every visit throughout the study (V1 to V13);
6. HbA1c: for screening only.

## 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 Determination of 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%.

### 9.2 Analysis Variables

#### 9.2.1 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:  $(\text{date of informed consent} - \text{date of birth})/365.25$
- Gender (male/female)
- Body weight (kg)
- Body Mass Index (BMI,  $\text{kg}/\text{m}^2$ ):  $\text{weight in kg}/(\text{height in meters})^2$
- Race

Disease characteristics including:

- Disease duration (years):  $(\text{date of informed consent} - \text{date of diagnosis})/365.25$
- APO-E genotype
- Baseline scores of ADAS-Cog, MMSE, ADCS-ADL, CDR/CDR-SB, and NPI
- 18F-AV-45 retention (SUVR)

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, CRP, ESR, TNF- $\alpha$ , IL-6, IL-8, and number of microhemorrhages in the brain will also be summarized.



### 9.2.2 Immunogenicity variables

The level of anti-A $\beta$  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 will be calculated for each arm.

### 9.2.3 Efficacy variables

#### 9.2.3.1 Rating scales

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.

#### 9.2.3.2 18F-AV-45 retention

18F-AV-45 PET scanning is performed at the second screening (S2), Week 52 (V10), and Week 78 (V13). No procedure for handling missing assessments will be applied if there is a missing value.

### 9.2.4 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 (HbA1c, glucose AC, AST, ALT, bilirubin, sodium, total protein, BUN, creatinine, potassium, and albumin), and inflammatory parameters (CRP, ESR, TNF- $\alpha$ , IL-6, and IL-8)

## 9.3 Analysis Populations

### 9.3.1 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.

### 9.3.2 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.

### 9.3.3 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 informed consent
- Randomized subjects: subjects who receive a randomization number via IVRS/IWRS
- The safety population (as defined in Section 9.3.2)
- The mITT population (as defined in Section 9.3.1)
- The PP population (as defined in Section 9.3.1)

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.

## 9.4 Statistical Methods

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.

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

#### 9.4.1 Demographic and baseline characteristics

##### *9.4.1.1 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 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 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.

##### *9.4.1.2 Previous and concomitant medications/therapy*

Medications will be classified into the following two groups:

- Previous medications are those that the subject took within 24 week 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.

##### *9.4.1.3 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 study center, treatment group, and overall.

#### 9.4.2 Treatment tolerability and compliance

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:

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

where

A: number of administered doses of completers

B<sub>1</sub>: number of administered doses of subject(s) who drops out due to drug-related AE(s)

B<sub>2</sub>: 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:

$$100\% \times (\text{Actual injection dose}/\text{Prescribed injection dose})$$

#### 9.4.3 Analysis of immunogenicity variable

Immunogenicity analyses will be performed on the mITT and PP populations. Response rate will be provided for the two active treatment groups (Arm 1 and Arm 2) and the placebo group (Arm 3). The change in antibody level will be analyzed by a repeated-measures mixed-effects model.

#### 9.4.4 Analysis of efficacy variables

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

#### 9.4.5 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 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.

#### *9.4.5.1 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 in each treatment group, 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 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 in each treatment group.

#### **Local tolerability at injection site**

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

#### **Vasogenic edema and amyloid imaging related abnormalities**

The number and percentage of subjects with amyloid-related imaging abnormalities (ARIA) will be summarized and presented by treatment group<sup>24</sup>.

#### *9.4.5.2 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 study drug 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 for each treatment group.

#### *9.4.5.3 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 for each treatment group.

#### *9.4.5.4 Analysis of 12-lead ECG status*

Only ECG status (i.e. normal or abnormal) will be reported.

#### *9.4.5.5 Reason for withdrawal*

Reason for withdrawal will be tabulated by study center, treatment group and overall.

## 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.

An Electronic Case Report Form (e-CRF) will be used in this study. Should a correction be made, the correction will be entered in the e-CRF overwriting the initial information. An audit trail will allow to identify the modification.

Data are available within the system to the sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the sponsor after receipt of the CRFs may generate additional requests to which the investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.



---

## **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 e-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 e-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.

## 15 REFERENCES

1. Jacobsen, J. S., Reinhart, P. & Pangalos, M. N. Current Concepts in Therapeutic Strategies Targeting Cognitive Decline and Disease Modification in Alzheimer's Disease. *NeuroRx* **2**, 612–626 (2005).
2. Rin H, Huang MG & Tseng MC Prevalence of elderly dementias in Taipei area. *Proc Ann Meeting Soc Neurol Psychiatry, ROC* **24** (1987).
3. Liu, H. C. *et al.* Prevalence and subtypes of dementia in Taiwan: a community survey of 5297 individuals. *J Am Geriatr Soc* **43**, 144–149 (1995).
4. Yip PK, Shyu TI & Lee JY Prevalence of dementia in the elderly in an urban district of Taipei. *Acta Neurol Sin* **1**, 347–354 (1992).
5. Liu, H. C. *et al.* Prevalence and subtypes of dementia in a rural Chinese population. *Alzheimer Dis Assoc Disord* **12**, 127–134 (1998).
6. Liu, C. K. *et al.* Prevalence of dementia in an urban area in taiwan. *J. Formos. Med. Assoc.* **95**, 762–768 (1996).
7. Liu, C. K. *et al.* Incidence and subtypes of dementia in southern Taiwan: impact of socio-demographic factors. *Neurology* **50**, 1572–1579 (1998).
8. Schenk, D., Hagen, M. & Seubert, P. Current progress in beta-amyloid immunotherapy. *Curr. Opin. Immunol.* **16**, 599–606 (2004).
9. Gilman, S. *et al.* Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology* **64**, 1553–1562 (2005).
10. Orgogozo, J.-M. *et al.* Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. *Neurology* **61**, 46–54 (2003).
11. Wang, C. Y. Immunogenic peptide composition for the prevention and treatment of Alzheimer's Disease. (2004).at <<http://webcache.googleusercontent.com/search?q=cache:ZcVbsodyWlgJ:www.freepatentsonline.com/y2004/0247612.html+&cd=2&hl=zh-TW&ct=clnk&client=firefox-a>>
12. Wang, C. Y. *et al.* Site-specific UBITH amyloid-beta vaccine for immunotherapy of Alzheimer's disease. *Vaccine* **25**, 3041–3052 (2007).
13. Agadjanyan, M. G. *et al.* Prototype Alzheimer's disease vaccine using the immunodominant B cell epitope from beta-amyloid and promiscuous T cell epitope pan HLA DR-binding peptide. *J. Immunol.* **174**, 1580–1586 (2005).
14. Cribbs, D. H. *et al.* Adjuvant-dependent modulation of Th1 and Th2 responses to immunization with beta-amyloid. *Int. Immunol.* **15**, 505–514 (2003).
15. Ranginwala, N. A., Hynan, L. S., Weiner, M. F. & White, C. L., 3rd Clinical criteria for the diagnosis of Alzheimer disease: still good after all these years. *Am J Geriatr Psychiatry* **16**, 384–388 (2008).

16. Löppönen, M., Räihä, I., Isoaho, R., Vahlberg, T. & Kivelä, S.-L. Diagnosing cognitive impairment and dementia in primary health care -- a more active approach is needed. *Age Ageing* **32**, 606–612 (2003).
17. Klunk, W. E. *et al.* Uncharged thioflavin-T derivatives bind to amyloid-beta protein with high affinity and readily enter the brain. *Life Sci.* **69**, 1471–1484 (2001).
18. Klunk, W. E. *et al.* Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann. Neurol.* **55**, 306–319 (2004).
19. Rinne, J. O. *et al.* 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. *Lancet Neurol* **9**, 363–372 (2010).
20. Eli Lilly and Company. Prescribing Information of Amyvid™. (2012).at <<http://pi.lilly.com/us/amyvid-uspi.pdf>>
21. Holmes, C. *et al.* Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. *Lancet* **372**, 216–223 (2008).
22. Mangialasche, F., Solomon, A., Winblad, B., Mecocci, P. & Kivipelto, M. Alzheimer's disease: clinical trials and drug development. *Lancet Neurol* **9**, 702–716 (2010).
23. Wang C. Y. *et al.* UB-311, a novel UBITH<sup>®</sup> amyloid  $\beta$  peptide vaccine for mild Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* **3**, 262-272 (2017)
24. Sperling, R. A. *et al.* Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. *Alzheimers Dement* (2011).doi:10.1016/j.jalz.2011.03.003

## **APPENDIX 1: IMAGING PROTOCOL**

### **1 Introduction**

Since amyloid-modifying therapeutic agents have entered Alzheimer’s disease (AD) clinical trials over the past decade, the occurrence of imaging abnormalities has required careful consideration by pharmaceutical companies and regulatory authorities. Brain imaging in AD has undergone revolutionary changes with the wide availability of an unprecedented array of new techniques. 18F-AV-45 positron emission tomography (PET) exhibits high affinity specific binding to amyloid plaques. Since a negative 18F-AV-45 PET scan result reduces the likelihood that a patient’s cognitive impairment is due to AD, it can be an adjunct to other diagnostic evaluations. Various magnetic resonance imaging (MRI) methods are typically used in clinical trials of mild cognitive impairment (MCI)/AD for three purposes: 1) Eligibility and enrichment; 2) Safety: monitor side effects related to the study drug. 3) Efficacy: provide quantitative imaging biomarkers to assess drug effects on neurodegeneration longitudinally.

It is standard practice in AD trials to exclude patients with radiological evidence of space-occupying lesions, major vascular disease or infarct. Since the clinical diagnosis of AD during life is frequently inaccurate outside of research centers, 18F-AV-45 PET may have value as an adjunct to clinical diagnosis. For some amyloid-modifying therapies, microhemorrhages are a risk factor for drug side effects. The safety MRI assessments focus on the recently described amyloid-related imaging abnormalities (ARIA) seen in therapies directed at amyloid pathway modification, “vasogenic edema” and/or sulcal effusion (ARIA-E) and hemosiderin deposits (ARIA-H), including microhemorrhages and superficial siderosis. The volumetric MRI (vMRI) acquisition and derived metrics assess the neurodegenerative consequences of the disease and potential therapeutic alteration on both regional and whole brain structures. Resting-state functional MRI (rs-fMRI) is an imaging method that reflects synaptic activity through changes in blood flow and the deoxyhemoglobin to oxyhemoglobin ratio, and the structures that are particularly vulnerable for early amyloid deposition in AD appear to overlap with the heteromodal cortices of the default mode network.

### **2 MRI Methods**

Each imaging site will be required to satisfy the requirements of MRI Site Qualification by completing a site specific technical evaluation form, completing imaging manual training and approval of all MRI scanners to be utilized for study subjects. Prior to site initiation, a MRI Imaging Manual, outlining image sequences and parameters will be created. All MRI imaging time points are to be acquired, reconstructed and submitted as described in the Imaging Manual. An Image Corelab will collect the MRI image data and an independent reviewer, with appropriate qualification, will make a qualitative and quantitative assessment of the screening MRI and safety MRI scans for each imaging time point.

#### **2.1 Screening MRI Scan**

Beside results of laboratory test and ECG, the brain imaging performed at screening visit or during the screening stage must be available and free of any clinically significant abnormalities likely to interfere with the study conduct or evaluations. For all the brain imaging studies, sites should operate under the local institution regulations and policies for patient management and care and provide scans in digital imaging and communication in medicine format and ideally be able to transfer via secure internet connection to the imaging core lab. MRI scans should be acquired on either 1.5 or 3.0 Tesla scanners manufactured by General Electric Company, Philips or Siemens. Toshiba scanners may also be considered but the equipment should be less than 10 years old. The subject positioning should remain unchanged throughout the MRI examination. Proper subject positioning is crucial for successful reproduction of serial MRI exams. Therefore, it is important that each subject is positioned in the same manner for each and every MRI exam.

*Exclusion criteria:* the first screening MRI scan with evidence of followings:

- Central nerves system (CNS) infection (e.g., neurosyphilis, acquired immune deficiency syndrome or prion disease);
- Major neurological disorder or degenerative conditions associated with significant cognitive impairment such as multiple sclerosis or Huntington's disease;
- Structural lesions (e.g., primary or secondary brain tumors, subdural hematoma or normal-pressure hydrocephalus);
- Severe traumatic brain injury;
- Cerebrovascular disease;
- Multiple infarction (at least 2 different arterial territories involved), or a large intracerebral infarct (>2 cm), or multiple lacunes, or lacunes in a critical memory structure (e.g., basal ganglia), or a large intracerebral hemorrhage (>2 cm) or more than four microhemorrhages; a single area of superficial siderosis;

## 2.2 Safety MRI

The purpose of safety MRI is used to monitor amyloid-related imaging abnormalities (ARIA) including vasogenic edema and sulcal effusions (ARIA-E) and microhaemorrhages and haemosiderin deposits (ARIA-H), as well as age-related white matter changes (ARWMC). Serial brain safety MRI scans should be performed regularly and at intervals of no more than every 3 months. The MRI will be performed at the first screening and at weeks 12, 24, 36, 48, 60, and 78 to assess ARIA that may be induced by amyloid-modifying therapy.

The Core MRI protocol consists of 3 types of sequences that are acquired in every subject and on every MRI vendor system, these are: (1) T1 weighted scan, (2) T2/ fluid attenuated inversion recovery (FLAIR), and (3) T2\*-gradient refocused echo (GRE). T2/FLAIR imaging demonstrates ARIA-E with increased signal while the appearance of ARIA-H can be observed on long echo time GRE (T2\*-GRE) sequences. The T2\*-GRE should have a minimum Echo Time (TE) of 20 ms or greater and slice thickness of 5 mm or less. Microhemorrhages typically manifest as a focal, round, very low intensity (relative to adjacent brain) lesion in the brain parenchyma, detected on an appropriately weighted (T2 or T2\*) MRI sequence, such as GRE sequences. Additional susceptibility weighting imaging (SWI) sequence may be imparted by post processing to improve microhemorrhages visualization, obtaining high quality multi-site data that is consistent over time, and across different MRI systems.



The Imaging Corelab will qualify (and re-qualify after upgrades) each scanner on the MRI protocol. Correct specific classes of image artifacts in each image acquired; imaging intensity non-uniformity, image warping due to gradient nonlinearity, and scaling changes over time.

### 3 18F-AV-45 PET Methods

Early phase human PET studies indicate that florbetapir binds to amyloid vulnerable brain regions in AD patients, similar to reported binding with <sup>11</sup>C Pittsburgh Compound B (<sup>11</sup>C-PiB) in AD, with minimal cortical binding in normal control subjects<sup>3</sup>. The high correspondence of florbetapir binding and Aβ amyloid plaque load has been reported in a postmortem series<sup>4</sup>.

Prior to site initiation, a PET Imaging Manual, outlining image acquisition and reconstruction parameters will be created. All PET imaging time points are to be acquired, reconstructed and submitted as described in the Imaging Manual. An Image Corelab will collect the PET image data and an independent reviewer, with appropriate qualification, will make a qualitative and quantitative assessment of the 18F-AV-45 PET amyloid deposition for each 18F-AV-45 PET imaging time point.

#### 3.1 PET/Computed Tomography (CT) Site Qualification

Each imaging site will be required to satisfy the requirements of PET Site Qualification by completing a site specific technical evaluation form, completing imaging manual training and approval of all PET/CT scanners to be utilized for study subjects. Phantom imaging data (i.e. uniformity, Hoffman, Hot Sphere) is to be submitted prior to screening (ideally prior to site initiation) and then quarterly throughout the remaining study period.

#### 3.2 PET/CT Imaging Visit

18F-AV-45 PET imaging will be acquired at the second stage screening and at week 52 and week 78 to assess the changes in Aβ burden from the baseline. Study subjects will receive a single intravenous bolus of approximately 370 MBq (10 mCi) of florbetapir (18F), followed by a 10-minute PET brain image, beginning approximately 50 minutes post-dose injection at each scan visit<sup>5</sup>. The subject should be supine with the head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Image reconstruction should include attenuation correction with resulting transaxial pixel sizes between 2 and 3 mm. In the event of scanning failure (i.e. excessive motion artifact, PET/CT scanner malfunction, or subject condition), the 18F-AV-45 PET/CT exam should be repeated.

#### 3.3 PET Central Independent Review

For the PET eligibility review, sites are required to submit screening 18F-AV-45 PET scans acquired during the second stage screening immediately to the Imaging Corelab to confirm the presence of amyloid deposition and study eligibility. An independent reviewer will confirm the presence of amyloid deposition on the PET scans by conducting a visually qualitative assessment and making a determination for Aβ+ (amyloid positive) or Aβ- (amyloid negative). The Independent Reviewer will make the determination of Aβ+ (amyloid positive) or Aβ- (amyloid negative) based on a standard uptake value ratio (SUVR) threshold cutoff value (qAb-)<sup>5</sup>.

Semi-quantitative visual rating 18F-AV-45 PET images will be conducted for each enrolled subject and all available visits: the Independent Reviewer (qualified nuclear medicine physician) will rate

each PET image independently for amyloid burden based on successive levels of 18F-AV-45 retention.

A quantitative analysis of PET image data will be performed utilizing PET software such as MIMNeuro for enrolled subjects and respective visits<sup>4</sup>. The 18F-AV-45 PET images will be fitted to region overlays to quantify the mean cortical to cerebellum SUVR calculated from cortical regions, such as frontal cortex, temporal cortex, precuneus, parietal cortex, anterior cingulate, and posterior cingulate, relative to the whole cerebellum reference region.

18F-AV-45 PET follow up visits will be acquired at week 52 and week 78 to assess the changes in A $\beta$  burden from the baseline. Semi-quantitative and quantitative analysis will be performed as described above.

#### 4 Volumetric Magnetic Resonance Imaging (vMRI) for the Research Study

Results of a study of vMRI versus cognitive testing demonstrate that vMRI could become the principal outcome measure for clinical trials in AD due to its precision<sup>6</sup>. The vMRI scan should cover the entire brain (including cerebellum) and skull, superiorly and laterally. In the anterior/posterior plane the nose should also be included, otherwise image folding will result and the exam may not be usable for the study. To ensure scanner stability and scan quality throughout the study, each site is required to perform on-going quality control scans on an MRI phantom (such as Alzheimer's disease neuroimaging initiative phantom, American College of Radiology-ACR phantom, etc.) using the localizer and 3D T1-weighted scan prior to site scanning their first subject (prior to the screening), and then semi-annually throughout the remaining study period, as well as after any hardware upgrades to the scanner. If a site fails to perform these phantom scans prior to scanning study subjects, the study coordinator and the principal investigator at each site should be notified.

The most important image set is the T1-weighted 3D volumetric acquisition. Isotropic voxels are desired to avoid a directional bias, but not required. The target voxel size is approximately 1 mm<sup>3</sup>, with a maximum of 1.5 mm in any one direction. The following is an example of a typical magnetization-prepared rapid gradient echo (MP-RAGE) sequence using a Siemens Trio 3-Tesla scanner for reference purpose: 128 slices, TR/TE = 2530/3.39 ms, slice thickness = 1.0 mm, flip angle = 7°, inversion time = 1100 ms, FOV = 256 × 256 mm, and in-plane matrix size = 256 × 256. Sites should acquire a 3D T1-weighted scan with scan parameters that are close to the MP-RAGE sequence mentioned above, compensating for differences in parameters based on their scanner manufacturer.

Proper placement in the head coil is crucial because scans are acquired straight, not in an oblique orientation. It is mandatory to use the same position at the time of baseline and all subsequent visits. Position on mid-sagittal slice from tri-planar scout and make sure to get full brain coverage without image wrap: the skull must be fully included superiorly and laterally and the entire cerebellum should be included inferiorly. Every subject for the study must receive a clinical check by an on-site radiologist at each MRI facility. A request for a repeat MRI may be required in the event that the scans are found to be unacceptable due to subject motion or an incomplete MRI acquisition. Repeat MRI scans should be performed as quickly as possible.

The vMRI data should be reviewed for quality at each site prior to sending the images to the Central Imaging Corelab, and if there are any artifacts, the scan should be repeated to get high quality images. Hippocampus and other brain regions (such as whole brain, ventricles) shall be assessed

using a semi-automatic, atlas based brain segmentation technique, and will be over-read by an independent reviewer (a qualified neuroradiologist), to capture volumetric measures. Volumetric data shall be corrected for differences in head size by dividing each measurement by the estimated total intracranial volume which is computed as the sum of the volumes of all four ventricles, the white matter, the gray matter, with the brain stem excluded.

The vMRI will be conducted at the first screening, at week 48 and week 78.

## 5 Resting state fMRI (rs-fMRI) for the Research Study

By measuring functional connectivity between spatially distinct brain regions, rs-fMRI can be used to evaluate brain function. Default mode network consists of the bilateral parietal cortex, the precuneus and posterior cingulate cortex, anterior cingulate cortex, medial prefrontal cortex, hippocampus, and thalamus<sup>7</sup>. Previous rs-fMRI studies have shown a disruption in functional connectivity between structures that are part of the default mode network at an early stage of AD and MCI<sup>8-10</sup>.

The higher resolution and shorter TR greatly enhances the ability to capture the spatial and temporal variations of brain activity and connectivity. The following is the recommended protocol: whole brain volume at  $2 \times 2 \times 2$  mm resolution within a TR of 720 ms and TE of 33-34.6 ms. It also requires the use of a 32 channel head coil (such as Nova Medical). Eyes open; 72 slices; 20.8 cm (A-P)  $\times$  18 cm (R-L) FOV; Matrix  $104 \times 90$ ; Flip angle  $52^\circ$ ; scan time:  $\sim 15$  min.

The rs-fMRI data will be pre-processed, including spatial smoothing with a 6 mm Gaussian kernel to produce default and attention networks robustly. The default mode network will be assessed by correlating each voxel in individual datasets with low frequency fluctuations within seed regions placed in the brain. This method correlates the average BOLD time course of voxels within these regions with each other and with the time courses of all other voxels in the brain.

The rs-fMRI should be conducted at the first screening, at week 48 and week 78.

## 6 Reference

1. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke; a journal of cerebral circulation*. 2001; 32(6):1318-1322.
2. Sperling RA, Jack CR, Jr., Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2011; 7(4):367-385.
3. Wong DF, Rosenberg PB, Zhou Y, et al. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand  $18\text{F-AV-45}$  (florbetapir [corrected] F 18). *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*. 2010; 51(6):913-920.

4. Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. *Jama*. 2011; 305(3):275-283.
5. Johnson KA, Sperling RA, Gidicsin CM, et al. Florbetapir (F18-AV-45) PET to assess amyloid burden in Alzheimer's disease dementia, mild cognitive impairment, and normal aging. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2013; 9(5 Suppl):S72-83.
6. Jack CR, Jr., Slomkowski M, Gracon S, et al. MRI as a biomarker of disease progression in a therapeutic trial of milameline for AD. *Neurology*. 2003; 60(2):253-260.
7. Damoiseaux JS, Rombouts SA, Barkhof F, et al. Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103(37):13848-13853.
8. He Y, Wang L, Zang Y, et al. Regional coherence changes in the early stages of Alzheimer's disease: a combined structural and resting-state functional MRI study. *NeuroImage*. 2007; 35(2):488-500.
9. Sorg C, Riedl V, Muhlau M, et al. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104(47):18760-18765.
10. Wang K, Liang M, Wang L, et al. Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. *Human brain mapping*. 2007; 28(10):967-978.

## **APPENDIX 2: RESEARCH STUDY PROTOCOL**

A Research Study Adjunctive to a Randomized, Double-blind, Placebo-controlled, 3-arm Parallel-group, Multicenter, Phase IIa Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of UBITH<sup>®</sup> AD Immunotherapeutic Vaccine (UB-311) in Patients with Mild Alzheimer's Disease (V203-AD). Protocol No.: V203-AD-Research.