

CLINICAL STUDY PROTOCOL

A Phase I, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Immunogenicity of AV-1959R in Healthy Participants

PROTOCOL NO. AU-AV1959R-101

Version No:	4.0
Protocol Date:	25 June 2024
Product:	AV-1959R
Phase:	Phase I
Sponsor:	Arvax Pty Ltd Level 5 63 Pirie Street Adelaide SA 5000

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Sponsor Signature Page**PROTOCOL NUMBER:** AU-AV1959R-101**PROTOCOL VERSION:** 4.0**PROTOCOL DATE:** 25 June 2024**PROTOCOL TITLE:** A Phase I, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Immunogenicity of AV-1959R in Healthy Participants

I, on behalf of Arvax Pty Ltd, approve this protocol and agree to comply with all requirements regarding the obligations of Sponsor and all other pertinent requirements of Good Clinical Practice (ICH E6, R2), the Declaration of Helsinki, and applicable regulatory requirements.

Sponsor's authorized signatory
Name and Title

Date

Investigator Signature Page**PROTOCOL NUMBER:** AU-AV1959R-101**PROTOCOL VERSION:** 4.0**PROTOCOL DATE:** 25 June 2024**PROTOCOL TITLE:** A Phase I, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Immunogenicity of AV-1959R in Healthy Participants.

By my signature below, I certify that I have read and understand the foregoing protocol and I agree to personally conduct or supervise the described investigation. I agree to conduct the study in accordance with the current protocol and in compliance with the Guidance on Good Clinical Practice (ICH, E6, R2), the Declaration of Helsinki, and applicable regulatory requirements.

I agree to the content of this protocol and the confidential nature of the documentation made a part of this study. I also acknowledge that Arvax Pty Ltd has the right to discontinue this study at any time.

Signature of Investigator

Date

Printed Name

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Protocol Synopsis

Protocol Number:	AU-AV1959R-101
Title:	A Phase I, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Immunogenicity of AV-1959R in Healthy Participants.
Study Phase:	1
Rationale:	<p>Alzheimer's disease (AD) is a neurodegenerative condition, clinically characterized by progressive impairment of memory and cognitive functions. The amyloid cascade hypothesis proposes that Aβ oligomer formation is a critical feature for the initiation of downstream pathological processes that include tau pathology, which is directly associated with neurodegeneration (inflammation, oxidative stress, and synaptic, neuronal loss) and cognitive decline. Immunotherapy is one of the most promising therapeutic strategies for AD prevention.</p> <p>AV-1959R is a cGMP-grade recombinant protein composed of three copies of the N-terminal region of human Aβ spanning amino acids 1-11 (Aβ₁₋₁₁) and an immunogenic vaccine platform composed of 12 foreign promiscuous T helper (Th) cell epitopes [one synthetic epitope and 11 epitopes from several microorganisms (tetanus; hepatitis B and influenza)] collectively designated as the MultiTEP vaccine platform.</p> <p>Advax-CpG55.2 is an adjuvant based on a combination of delta inulin and CpG55.2, that has been tested in combination with different vaccines in 10 human clinical trials, conducted in USA, Australia and Iran, involving >26,000 administrations to >13,000 individual subjects across the Phase 1, 2, 3 and booster study trials.</p> <p>Adjuvanted AV-1959R was extensively studied in multiple pre-clinical safety and efficacy studies in mice, rabbits, non-human primates (NHP). Delivered intramuscularly (IM) this vaccine generates robust cellular immune responses to foreign epitopes avoiding activation of potentially harmful autoreactive T cells and induces high titers of therapeutically potent anti-Aβ antibodies in mice, rabbits and NHP (1, 2). In safety toxicology studies, there were no adverse findings in health observations, food intake, body weights, gross necropsy, absolute organ weights or weigh ratios, clinical pathology or the histopathology data attributed to IM administration of a mouse model of AD. In initial Phase I trial, Sponsor will seek to determine the safety and immunogenicity of the adjuvanted vaccine in healthy participants.</p> <p>The proposed Phase I study is a single-center, double-blind, randomized, placebo-controlled trial to determine the safety and tolerability of AV-1959R at 100 μg and 300 μg doses or placebo (formulation without active ingredient) both formulated with Advax-CpG55.2 via IM administration in healthy participants. Each participant will be immunized at Weeks 0, 4 and 14 and undergo follow-up period of 8-weeks post last immunization.</p>
Objectives:	<p>Primary objective:</p> <ul style="list-style-type: none"> To determine the safety and tolerability of adjuvanted AV-1959R vaccine compared to placebo in healthy participants. <p>Secondary objective:</p> <ul style="list-style-type: none"> To evaluate the immunogenicity of the adjuvanted AV- 1959R vaccine by assessing the level of humoral immune responses (anti-Aβ antibody levels: IgM and IgG isotypes and IgG1, IgG2, IgG3, and IgG4 subclasses) in plasma.
Subject Population:	This study will enroll up to 16 healthy volunteers.

Study Duration:	Approximately up to 26 weeks (4 weeks [Screening period] + 14 weeks [Treatment period] + 8 weeks [Follow-up, i.e., 56±7 days after the last dose of IP])
Study Design:	<p>This is a Phase 1, randomized, double-blind, placebo-controlled, multiple dose-escalating trial consisting of 2 ascending dose cohorts in healthy male and female participants, 40-60 years of age.</p> <p>Subjects will undergo Screening visits within 4 weeks (up to 28 days) prior to the administration of the investigational product (IP) as per Table 1 to identify eligible participants. Screening procedures may be performed in two or more screening visits. MRI examination for determination of subject eligibility will be performed at the later stage of screening.</p> <p>A total of sixteen (16) subjects will be enrolled into the study in one of two dose cohorts. Eligible participants will be randomly assigned in a 3:1 ratio to receive 3 intramuscular injections of either AV-1959R or placebo both formulated with Advax-CpG55.2 adjuvant at baseline (Week 0), Weeks 4 and 14 and undergo follow-up visit at Week 22 (Table 1). Each cohort will contain up to 8 subjects; six (6) will be randomly assigned to receive AV-1959R and two (2) participants to receive a placebo. The following doses will be administered at each immunization time point:</p> <ul style="list-style-type: none"> • Cohort 1: 100 µg of AV-1959R or placebo • Cohort 2: 300 µg of AV-1959R or placebo <p>A Safety Review Committee (SRC) will be established to review the study progress, provide oversight for the determination of the safety of dose escalation, and determine if it is appropriate to continue the study or modify the protocol. Should the SRC choose not to escalate to the next dose level, previous dose level may be repeated if deemed necessary.</p> <p>Dose-limiting toxicity (DLT) will be monitored during the entire study. DLT is defined as a serious or severe clinically significant AE (CTCAE Grade 3 or higher) not resolving within 14 days after each immunization in the dosing cohort that may be considered by the Investigator to be related to the study drug.</p> <p>For each dose level, dosing will be staggered such that 2 subjects will be dosed prior to the rest of the group. Initially, 2 subjects (one active and one placebo) in each Cohort will be dosed (Immunization #1, Day 0) prior to the rest of the cohort. General tolerability to treatment will be monitored over 14 days following each immunization of AV-1959R or placebo by the Investigator. If the safety assessments (AEs, clinical laboratory test results, vital sign measurements, 12 lead ECG results, and physical examination) are acceptable based on the judgement of the Investigator on Day 15±2 and Day 42±3, individual participants will receive Immunization # 2 (Day 28±2) and Immunization # 3 (Day 98±5), respectively as planned.</p> <p>Investigator will also determine whether the remaining 6 subjects (five active and one placebo) in the Cohort will be dosed after review of a minimum of 14 days safety assessments (AEs, clinical laboratory test results, vital sign measurements, ECG results, and physical examination) following first immunization of AV-1959R or placebo in sentinel group.</p> <p>Dose escalation decision will be made by SRC based upon review of adverse events (AEs) and all safety data from 14 days after the first immunization of all 8 participants in first cohort before escalation to the second dose cohort.</p>

	<p>Dose escalation will be determined by the number of subjects experiencing DLT not resolving within 14 days after first immunization:</p> <ul style="list-style-type: none"> • If ≤ 1 participant experienced a DLT two weeks after the first immunization, then initiation of the second dose (300μg) cohort may proceed. • If ≥ 2 participants experience DLT in two weeks after the first immunization, then no further dose increase will occur. <p>Dose escalation will be suspended or stopped if any of the following occurs:</p> <ul style="list-style-type: none"> • Death from any cause other than events clearly unrelated to the study drug; • Any CTCAE Grade 3 or higher adverse event that certainly, probably/likely or possibly related to the study drug and persists for more than two weeks; • Any serious or severe clinically significant AE (CTCAE Grade 3 or higher) that certainly, probably/likely or possibly related to the study drug and occurs within 4 weeks after product administration; • Any other event(s) that in the opinion of the Investigator should invoke suspension of further enrollment. <p>Based on information of occurred DLT events, the SRC may at any time decide to terminate the study and the sponsor will submit appropriate reports to HREC and TGA.</p> <p>A local screening MRI will be performed at screening and then at Week 22 as safety measure. The MRI scans will be reviewed by the Investigator or qualified designee for immediate participant management.</p>
Inclusion Criteria:	<p>A subject must meet all of the following inclusion criteria to participate in this study:</p> <ol style="list-style-type: none"> 1. Healthy, adult, male or female of non-childbearing potential, 40 to 60 years of age, inclusive, at Screening visit. 2. Body mass index (BMI) ≥ 18.0 and ≤ 32.0 kg/m² at Screening visit 3. Medically healthy with no clinically significant medical history, abnormalities in physical examination, laboratory variables, vital signs, ECG or MRI at the time of Screening and Baseline (if applicable), as deemed by the Investigator or designee. 4. Signed informed consent form by the participant prior to initiation of any study-related procedures. 5. If female of non-childbearing potential, must meet at least one of the following criteria: <ol style="list-style-type: none"> a. post-menopausal status defined as amenorrhea for at least 12 months prior to study drug dosing in absence of any exogenous hormonal treatments and follicle stimulating hormone (FSH) levels in the laboratory defined post-menopausal range. b. subject report of surgical sterilization (i.e., hysterectomy, bilateral tubal ligation, bilateral oophorectomy/ salpingectomy) at least 6 weeks prior to Day 1. Documented evidence of surgical sterilization is required. 6. If male, must have had a vasectomy 90 days prior to the Screening visit with a follow up negative sperm count, or agree to not donate sperm for 90 days after the last dose of study drug and, if engaging in vaginal sexual intercourse with a female partner of childbearing potential, agree to use a condom in addition to the female partner must use a highly effective method of birth control (e.g. intrauterine device, diaphragm, hormonal contraceptives) throughout the duration of the study treatment period and for 90 days after the last dose of study drug. Abstinence from heterosexual intercourse is an acceptable method of contraception. Subjects with same-sex partners (abstinence

	<p>from penile-vaginal intercourse) are eligible without needing contraception when this is their usual form of sexual relations.</p> <p>7. Ability, in the opinion of the investigator, to understand the nature of the trial and comply with protocol requirements, including the prescribed dosage regimens, scheduled visits, laboratory tests, and other trial procedures.</p>
Exclusion Criteria:	<p>A subject will be excluded from participation in this study if he or she meets any of the following criteria:</p> <ol style="list-style-type: none"> Any clinically significant medical history or observations at the time of Screening visit not specifically excluded in other criteria that, in the opinion of the Investigator or designee, may confound the results of the study, compromise the safety of the subject or otherwise render the subject unsuitable for participation. Magnetic resonance imaging (MRI) showing evidence of any of the following at the Screening: <ul style="list-style-type: none"> 1 or more small non-cortical lacunar infarct greater than 1.0 cm Any territorial infarct including acute or chronic Subjects who have microbleeds and areas of leptomeningeal hemosiderosis Subjects who have a presence of any other significant cerebral abnormalities, including ARIA-E, as assessed in the screening MRI scan. Contraindications for MRI scanning, including implanted metallic devices (e.g., non-MRI-safe cardiac pacemaker or neurostimulator; some artificial joints metal pins; surgical clips; or other implanted metal parts), or claustrophobia or discomfort in confined spaces. Any serious illness requiring systemic treatment and/or hospitalization within 4 weeks prior to study entry. History/evidence of clinically relevant pathology related to the cardiovascular system, respiratory tract, gastrointestinal tract, endocrinology, immunology, hematology, or any other systemic disorder/major surgeries that, in the opinion of the Investigator, would confound participation and follow-up. History or presence of any of the following: <ul style="list-style-type: none"> clinically significant acute illness or surgery within the previous 3 months of Day 1. hypersensitivity reaction or anaphylaxis to any medication to be of clinical significance to the current study or compromise the safety of the subject in the opinion of the Investigator history or suspicion of routine or chronic drug or alcohol abuse or dependence within 1 year prior to Day 1 based on subject report; excessive alcohol intake (defined as routine weekly intake of greater than 21 glasses/units per week, with one unit=150 mL of wine or 360 mL of beer or 45 mL of 45% alcohol). Clinically significant laboratory abnormalities at Screening visit, including (but not limited to): <ul style="list-style-type: none"> hemoglobin, hematocrit, total white blood count (WBC) or platelet count below the lower limit of the normal range alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >1.5 times the upper limit of the normal range serum creatinine above the upper limit of the normal range or estimated creatinine clearance <90 mL/minute as calculated by the Cockcroft-Gault equation

	<ul style="list-style-type: none"> ○ positive testing for human immunodeficiency virus (HIV-1 or -2), hepatitis B surface antigen (HBsAg), or positive testing for hepatitis C (HCV) <p>Clinical laboratory tests may be repeated as per Investigator's discretion.</p> <ol style="list-style-type: none"> 8. Systolic blood pressure (BP) >160 millimeters of mercury (mmHg), or <90 mmHg; diastolic BP >95 mmHg or <50 mmHg blood at Screening visit or Day 1. Vital signs may be repeated as per Investigator's judgement. 9. Supine heart rate less than 45 beats per minute (bpm) or higher than 100 bpm at the Screening visit or Day 1. Vital signs may be repeated as per Investigator's judgement. 10. ECG with QTcF interval duration equal or greater than 450 msec for males and 470 msec for females obtained after at least 5 minutes in a supine or semi-recumbent position at quiet rest at Screening visit or Day 1. 11. Any other medical, psychological, or social condition that, in the opinion of the Investigator, would prevent the participant from fully participating in the study would represent a concern for study compliance or would constitute a safety concern to the participant. 12. Participation in another investigational drug study or treatment with an investigational drug within 30 days or 5 half-lives, whichever is longer, before dosing. 13. Prior administration of any tau or amyloid-beta immunotherapy (vaccine, antibody) within 1 year prior to Screening. 14. The use of immunomodulatory or growth-stimulating factors such as systemic corticosteroids, cyclosporine, methotrexate, azathioprine, anti-CD25 antibody, GM-CSF, C-CSF, interferon (IFN), or interleukin-2 (IL-2) within 30 days prior to study entry. 15. Chronic use (>3 months) of warfarin, other coumarin derivatives, anticoagulants, or an anti-platelet agent (e.g., clopidogrel). 16. Parenteral use of immunoglobulin preparations, blood products, and plasma derivatives. 17. History/evidence of severe local or systemic reactions to vaccination or significant allergic reactions. 18. Female of childbearing potential. 19. Any skin condition and/or tattoo that may interfere with the evaluation of safety at the injection site. 20. Donation of blood or significant blood loss greater than 400 ml within the last 30 days prior to dosing.
Investigational Product, Reference Therapy, Dose, Mode of Administration, and Dose Regimen:	<p><u>Active:</u> AV-1959R, 100 µg, 300 µg plus adjuvant per immunization</p> <p><u>Placebo:</u> Normal saline solution (without active compound) plus adjuvant</p> <p><u>Adjuvant:</u> Advax-CpG55.2 [Advax-15mg, and CpG-0.15mg] combination adjuvant comprising delta inulin and CpG55.2 (Vaxine Pty. Ltd)</p> <p><u>Dosing regimen:</u> Three immunizations will be administered at Weeks 0, 4 and 14.</p> <p><u>Mode of administration:</u> Intramuscular (IM) injection.</p>
Study Outcomes Measures:	<p><u>Primary Outcome</u></p> <ul style="list-style-type: none"> ● The number of participants with Treatment-Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs). <p><u>Secondary Outcomes</u></p> <ul style="list-style-type: none"> ● Number of participants with clinically significant changes in vital signs. ● Number of participants with clinically significant changes in ECG results. ● Number of participants with clinically significant changes in laboratory tests.

	<ul style="list-style-type: none"> • Number of participants with clinically significant changes in physical examinations. • Immunological Outcomes: <ul style="list-style-type: none"> ○ Serum anti- Aβ and anti-MultiTEP antibodies concentrations, i.e., IgM, total IgG and IgG subclasses (IgG1, IgG2, IgG3, and IgG4)
Statistical Considerations:	<p>Up to 16 subjects will be enrolled in this study. The sample size was chosen pragmatically based on clinical considerations and considered sufficient for the safety objectives of this study, in which subjects will receive the investigational product in sequential ascending doses.</p> <p>Descriptive statistical analyses, including graphs, will be based on the different dosing cohorts. Each participant will be coded as valid or not valid for safety and immunogenicity evaluation before unblinding the results. Categorical variables will be summarized in frequency tables (n, %), by treatment group and dose. Continuous variables will be summarized using descriptive statistics. Demographic and baseline characteristics will be summarized overall for all participants. The number who enrolled in the study, who discontinued, and reasons for discontinuation will be presented. Data will also be presented in individual listings.</p>
Safety Analysis:	<p>Safety will be evaluated in terms of reported AEs and other clinical observations, clinical laboratory test results (hematology, serum chemistry, coagulation, and urinalysis), vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature), 12-lead safety ECG results, neurological and physical examination findings, MRI results.</p> <p>Treatment-emergent AEs will be coded using the latest version of MedDRA by System Organ Class (SOC) and Preferred Term (PT), classified from verbatim terms. The duration of TEAEs will be determined and included in listings, along with the action taken and outcome. ECG, vital signs and safety laboratory parameters will be summarized at each scheduled time point using descriptive statistics. Post-dose assessments will be compared with baseline measurements. The incidence of laboratory abnormalities will be summarized. Physical examination findings will be presented in listings.</p>
Immunological Analysis:	<p>The immunogenicity variables (antibody titers) will be summarized in listings and tables as absolute values and changes from baseline and graphically presented by time profiles. For each treatment group, geometric mean titers (GMTs) of the serum anti- Aβ antibodies along with their associated 95% confidence intervals (CIs) will be calculated. In addition, median, minimum, and maximum values will be calculated for each vaccine group at each time point.</p>

Table 1. Schedule of Assessments

Study Period ►	Screening Period ^a	Check-In	Treatment Period								Follow-up Period		
Assessment ▼ Study Day ►	Days -28 to -2	D -1	D1	D2	D15 ±2	D28 ±2	D29 ±2	D42 ±3	D98 ±5	D99 ±5	D112 ±5	D140 ±5	D154 ±7 or 56 ±7 days after the last dose
			Baseline	Phone Call ^b			Phone Call ^b		EOT	Phone Call ^b			EOS / ET
Study Week ►	Weeks -4 to 0	0	0		2	4		6	14		16	20	22
Informed Consent	x												
Demographics	x												
Eligibility	x	x ^c	x ^{c, p}										
Medical History, and update ^d	x		x ^p										
Height/Weight/BMI ^e	x												x
Physical Examination ^f	x				x	x		x	x				x
12-Lead ECG ^g	x		x		x	x		x	x		x	x	x
Vital Signs ⁱ	x		x		x	x		x	x		x	x	x
Viral Serology	x												
Pregnancy test (females)	x	x				x ^p			x ^p				x
Specimen collection (Chemistry, Hematology, Coagulation and Urinalysis)	x	x			x	x ^p		x	x ^p		x		x
Alcohol and drug testing	x		x ^p			x ^p			x ^p				
MRI Examination ^j	x												x
Randomization			x ^p										
IP Administration - immunization number ^k			x(1)			x(2)			x(3)				
Local Tolerability ^l			x			x			x				
Blood collection for anti- Aβ and anti-MultiTEP antibodies ^m			x ^p					x	x ^p		x	x	x
Prior and Concomitant Treatments ⁿ	←──												

Abbreviations: A β =amyloid-beta protein; BMI=body mass index; D=day; ECG=electrocardiogram; EOT=end of treatment; EOS=end of study; ET=early termination; MRI=magnetic resonance imaging.

^a Screening period will occur within 28 days prior to participant randomization on Day 1. Screening procedures may be performed in two or more screening visits. Extension of screening period beyond the 28 days window to allow completion of screening procedures may be permitted after discussion between the Investigator and the Medical Monitor on a case-by-case basis.

^b Subjects will be contacted via phone call, internet/web, or other acceptable means of communication and will be questioned for assessment of adverse events the next day after each IP dosing in the trial.

^c Inclusion/exclusion criteria will be reassessed on Day -1 and Day 1 (pre-dose) to ensure ongoing participant eligibility.

- ^d Medical occurrences that begin before the start of IP dosing but after obtaining informed consent will be recorded as medical history.
- ^e Height measurement and BMI calculation are required only at Screening. Body weight will be obtained with the participant's shoes off, jacket or coat removed.
- ^f Complete physical and neurological examinations should be completed at Screening, Days 42 and 154 (or EOS/ET). A symptom-directed examination) should be completed at Days 15, 28 and 98. Additional physical and/or neurological examinations may be done at any time point during the trial at the investigator's discretion.
- ^g 12-Lead ECG assessments will be performed after the participant has been supine and at rest for approximately 5 minutes. 12-lead ECGs on Immunization Days will be obtained within 30 minutes before and 4 hours post-immunization. Additional ECGs can be performed at the investigator's discretion (eg, if abnormalities are noted).
- ⁱ Vital signs will be measured after the participant has been supine and at rest for approximately 5 minutes. Vital signs on Immunization Days will be measured within 15 minutes before and at 15 min, 1 hour, 2 hours and 4 hours post-immunization. Additional vitals can be performed at the investigator's discretion (eg, if abnormalities are noted).
- ^j MRI examination will be performed for the detection of vasogenic edema, superficial siderosis, microhemorrhages, and macrohemorrhages, lacunar and cortical infarcts and other imaging abnormalities. MRI examination at Screening should be performed at the latest stage of the screening.
- ^k Subject will be randomized to the treatment on Day 1 upon eligibility confirmation prior to 1st immunization.
- ^l Assessments of injection site reactions on Immunization Days will be performed at 30 min, 1 hour, 2 hours and 4 hours post-dose (± 15 minutes), and more frequently, if deemed necessary by the investigator. Assessments of injection site on other days will be performed in subjects who have unresolved injection site AEs.
- ^m Blood will be collected for immunological assessment (detection of antibodies specific to A β) and stored at the clinical site.
- ⁿ Concomitant medications should be recorded from Screening through the participant's last visit/contact.
- ^o Adverse events (serious and nonserious) will be recorded from the informed consent through the participant's last visit/contact.
- ^p Procedure will be performed prior to immunization.

List of Abbreviations

Abbreviation	Definition
3xTg-AD	Triple transgenic mice, expressing human APP, PSEN1, MAPT
A β	Amyloid-beta, peptide derived from APP
A β 11	Peptide spanning 1-11 amino acids of APP
A β 42	Amyloid-beta 1-42 peptide derived from APP (spanning 671-713 amino acids) cleaved with β and γ secretases
AD	Alzheimer's disease
ADL	Activities of daily living
AE	Adverse event
APC	Antigen presenting cells
APP	Amyloid Precursor Protein
APP/Tg	Transgenic mice, expressing human APP
ARIA	Amyloid-related imaging abnormalities
APS	Amyloid probability score
BMI	Body mass index
CAA	Cerebral amyloid angiopathy
CDR	Clinical dementia rating
CFR	Code of Federal Regulations
cGMP	Current good manufacturing practice
CNS	Central nervous system
CRA	Clinical research associate
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTN	Clinical Trial Notification
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOT	End of treatment
EOS	End of study
ET	Early termination
eCRF	Electronic case report form
FAT	Fast axonal transport

FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFAP	Glial fibrillary acidic protein
GM-CSF	Granulocyte macrophage colony-stimulating factor
GMT	Geometrical mean titers
HIPAA	Health Insurance Portability and Accountability Act
HREC	Human Research Ethical Committee
HLA-DR	MHC class II cell surface receptor
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Intradermal
IgG	Immunoglobulin G
IM	Intramuscular
INR	International normalized ratio
IP	Investigational product
ISF	Investigator's site file
IV	Intravenous
kg	Kilogram
MCI	Mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCS	Not clinically significant
NfL	Neurofilament light chain
NIA	National Institute on Aging
NIH	National Institute of Health
NMDA	N-methyl-D-aspartate
PCS	Potentially clinically significant
PAD	Phosphatase activating domain
PBMC	Peripheral blood mononuclear cells
PET	Positron emission tomography
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedure

SRC	Safety Review Committee
SSRIs	Selective serotonin reuptake inhibitors
SNRIs	serotonin norepinephrine re-uptake inhibitors
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
US	United States
WMS-R LM-II	Wechsler Memory Scale-Revised Logical Memory subscale II

1. Introduction

1.1 Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized clinically by deterioration of memory and cognition, progressive impairment of activities of daily living (ADL) and a variety of behavioral disturbances. According to the World Health Organization (WHO), there are an estimated 47 million people with dementia worldwide, and there are 10 million new cases every year. AD is the most common cause of dementia and may contribute to 60-70% of all dementia cases. (3, 4, 5) This enormous and increasing worldwide healthcare burden due to AD, combined with a lack of effective treatments, indicate that new prophylactic and/or therapeutic approaches for treating AD are essential. In some patients with early or mid-stage AD, cholinesterase inhibitors, such as donepezil hydrochloride, may slow the progressive decline of memory and cognitive function. Another class of drugs that block NMDA glutamate receptors (e.g., memantine) has shown some improvement in patients with moderate to severe symptoms of confusion and memory loss. Additionally, there are drugs available that help to control some of the behavioral symptoms of AD such as sleeplessness, anxiety, and depression. However, currently there are no effective disease-modifying drugs that halt or reverse AD. The key neuropathological findings of AD are the accumulation of diffuse and neuritic plaques, mainly comprised of amyloid beta 40-43 amino acid peptides ($A\beta$), which are cleaved from amyloid precursor protein (APP) by β - and γ -secretases (6, 7, 8) and neurofibrillary tangles, consisting of hyperphosphorylated cytoskeletal microtubule (MT) associated protein, (9, 10, 11) Profound loss of neuronal synapses and cells, particularly of cholinergic neurons, gliosis, and inflammation are also apparent (12).

In AD, it has become increasingly recognized that amyloid accumulation in the brain occurs decades before such symptoms as memory loss and personality change begin. Current data suggest that $A\beta$ pathology emerges prior to Tau pathology and may accelerate toxic oligomers and neurofibrillary tangle formation (aggregates) (13, 14, 15, 16).

1.2 Investigational Product: adjuvanted recombinant protein vaccine, AV-1959R

AV-1959R is a cGMP-grade recombinant protein composed of three copies of the N-terminal region of human $A\beta$ and an immunogenic vaccine platform composed of 12 foreign promiscuous T helper (Th) cell epitopes [one synthetic epitope and 11 epitopes from several microorganisms (tetanus toxin; hepatitis B and influenza viruses)] collectively designated as the MultiTEP vaccine platform ([Figure 1](#)).

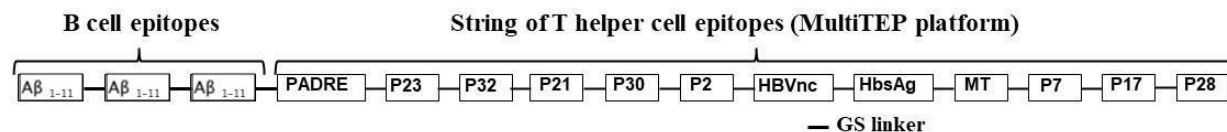


Figure 1. Schematic representations of AV-1959R vaccine construct.

AV-1959R encodes 3 copies of Aβ₁₋₁₁ fused to MultiTEP, one universal synthetic Th epitope, PADRE and eleven foreign promiscuous Th epitopes from infectious agents.

The MultiTEP is a string of twelve foreign T helper (Th) epitopes composed of one promiscuous synthetic (PADRE) peptide and eleven peptides from microorganisms (Tetanus, HBV, Flu) that most adults would have either been exposed to or vaccinated against. (1, 2, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28) These Th cell epitopes bind to various human MHC class II molecules (aka “immune response genes” termed HLA-DR/DQ/DP). AV-1959R formulated with Advax-CpG55.2 adjuvant (aka AdvaxCpG) generated strong anti-Aβ₁₋₁₁ antibody responses in wildtype mice and AD mouse models and reduced Aβ pathology in the bigenic mouse model of AD without any adverse findings attributed to the adjuvanted AV-1959R. (1, 2).

To enhance the immunogenicity of AV-1959R the Advax-CpG55.2 (Vaxine Pty. Ltd) adjuvant is planned to be used in this trial. Advax-CpG55.2 is manufactured from plant derived delta inulin plus synthetic CpG55.2 oligonucleotide. Vaccines containing Advax-CpG55.2 adjuvant have been tested in 10 human clinical trials, conducted in USA, Australia and Iran. Advax-CpG-55.2 adjuvant has been safely administered to human subjects, involving >26,000 administrations to >13,000 individual subjects across the Phase 1 (30 subjects received active vaccine), Phase 2 (300 subjects received active vaccine) Phase 3 (12,757 subjects received active vaccine) and Booster study (250 subjects received active vaccine) trials. Symptoms reported by study subjects receiving vaccines containing Advax-CpG55.2 adjuvant are consistent with those reported following administration of other licensed adjuvants, with injection site tenderness, redness and swelling being the most common local adverse events and headache, fatigue and myalgia being the most common systemic adverse events. These and other solicited reactions were predominantly mild and self-limited. No pattern of clinically significant changes in any hematological or biochemical parameters has been observed in subjects immunized with vaccines containing Advax-CpG55.2 adjuvant. (29, 30, 31, 32, 33, 34, 35) AV- 1959R at 100 µg/animal dose formulated in Advax-CpG-55.2 adjuvant, induced production of high titers of anti-Aβ antibodies in non-human primates (36).

No pattern of clinically significant changes in any hematological or biochemical parameters has been observed in subjects immunized with vaccines containing Advax-CpG55.2 adjuvant. These trials have provided collective data to support the safety, tolerability, and potency of Advax- CpG55.2 adjuvant.

1.3 Study Rationale

AD is a complex and multifactorial disease involving various genetic and environmental risk factors that lead to the development of two hallmark pathologies: A β soluble oligomers/fibrils/ plaques and soluble tau aggregates and neurofibrillary tangles (NFT) followed by inflammation and severe neurodegeneration. Findings that mutations in APP and PS1/PS2 that alter A β metabolism are tightly linked to inherited forms of AD and that up to 75% of adults with Down syndrome develop AD-like dementia strongly support the "amyloid cascade" hypothesis. (37, 38, 39) Genetic and postmortem data and neuroimaging studies in preclinical AD people and patients with MCI/AD indicate that A β deposition precedes cortical tau accumulation and drives tau-mediated neurodegeneration in AD. (40, 41). Not surprisingly, the development of potential therapies for AD has been focused largely on reducing pathological A β or tau and, more recently, on associated inflammation in the brain. Various groups tested A β /tau immunotherapeutics in clinical settings with mixed results, indicating that there is not much clinical benefit, likely because it is initiated in people with already developed AD. (42, 43, 44, 45, 46, 47) Although the development of AD therapeutics has still focused on targeting A β /tau pathology, a fair number of preclinical research suggest other important targets (e.g., pathological effects of cholesterol metabolism, ApoE, the endocytic system, microglial activation, etc.). Accordingly, various groups are working on the development of novel therapeutics associated with or not linked to pathological A β /tau accumulation in the brain. (48) Nevertheless, the mountains of pathophysiological and genetic data indicate that A β /tau are the best targets for the preventive treatment of AD, defined as delaying the onset of the disease. (2, 17, 23, 28, 49, 50, 51, 52)

As it was reported previously, antibodies against A β delayed A β ₄₂ oligomerization/fibrillization but did not prevent oligomer formation. Importantly, the same antibodies disaggregate preformed fibrils into small aggregates that are even more toxic than fibrils/plaques. (50) Later it was demonstrated that only preventive vaccinations reduced AD-like pathology and behavioral deficits in immunized mouse models of AD. (49) These data have been supported by preclinical data published by other groups (53, 54, 55, 56) and results from active and passive immunotherapy trials. (44, 45, 57, 58, 59, 60)

In this Phase I trial, Sponsor will seek to determine the safety, tolerability, and immunogenicity of an active preventive vaccine, AV-1959R, targeting N-terminus of amyloid beta in healthy participants.

1.4 Target population and participants selection strategy

Hallmarks of AD are the amyloid plaques consisting of early accumulation of oligomeric and fibrillar A β and, later in this disease, neurofibrillary Tau tangles. Importantly, AD is a progressive disease and, in regard to clinical scores, a highly variable disease. Nevertheless, data from the A4 prevention trial of late-onset AD (preclinical stage) showed that even before an amyloid scan turns positive, subthreshold accumulation of A β correlates with subtle memory deficits and presages future decline (61). Published data and current results from pre-clinical studies (49, 50), and clinical trials (62, 63, 64) indicate that AD vaccine targeting pathological A β may not be therapeutic if vaccination is initiated in patients with advanced pathologic stage of AD with neurodegeneration, particularly synapse loss, (65) Importantly, recent results of an A β immunotherapy clinical trial demonstrated that monoclonal antibodies are effective if they are administered in early AD patients (66, 67, 68, 69), and two amyloid beta-directed antibodies, aducanumab and lecanemab-irmb (BAN2401), have shown promising results and have got the FDA approval under the Accelerated Approval Pathway.

Not surprisingly, the development of potential therapies for AD has been focused largely on reducing pathological A β or tau and, more recently, on inflammation. However, various groups tested A β immunotherapeutics in clinical settings with mixed results, indicating that the clinical benefit is less likely if the treatment was initiated as a therapeutic measure in diseased people. (42, 43, 44, 45, 46, 47, 60, 70, 71, 72). Therefore, AD immunotherapeutic development has shifted from treatment to prevention, consistent with our long-standing theory, (2, 49, 50, 52) that safe and immunogenic preventive vaccine should be initiated in unimpaired people at risk of AD with biomarker evidence of Alzheimer's pathology. (64)

Therefore, the primary indication for the envisioned vaccine is for prevention or delay of onset of AD, postpone cognitive impairment. In this protocol, we suggest evaluating the safety and tolerability of the first-in-human adjuvanted A β vaccine, AV-1959R in healthy volunteers.

1.5 Mechanism of Action

Data demonstrated that the AV-1959R formulated with AdvaxCpG adjuvant, which has been shown to be safe and effective in human trials, (73, 74, 75, 76) is highly immunogenic not only in wildtype mice but also in bigenic mouse model of AD exhibiting both A β and tau pathologies as well as rabbits and non-human primates. AV-1959R vaccine was safe and generated high titers of antibodies against A β as

evidence by the reduction of A β pathology in the brains of vaccinated mouse models of disease. (2) Delivered intramuscularly this adjuvanted vaccine generated robust cellular immune responses to foreign T helper epitopes avoiding activation of potentially harmful autoreactive T cells and induced high titers of a therapeutically potent antibody specific to pathological A β in all animal models.

Immunogenicity and overall safety profile of cGMP AV-1959R vaccine were evaluated in rabbits and monkeys. These studies demonstrated that adjuvanted AV-1959R vaccine generates robust anti-A β antibodies without inducing potentially harmful Th cell responses specific to self-A β peptide (i.e., autoreactive T cells).

Thus, data generated with MultiTEP-based vaccines for neurodegenerative diseases in mouse models of AD/PD, rabbits, and monkeys. (1, 2, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28) suggest that in vaccinated participants AV-1959R can potentially overcome high polymorphism of MHC class II genes by activating a broad repertoire of naïve and memory Th cells specific to carrier (MultiTEP):

- i. Could induce high titers of antibodies against the self B cell epitope, A β 1-11, and only low titers of antibodies specific to the vaccine platform itself.
- ii. Could generate therapeutic anti-A β antibodies in the vast majority of immunized people.
- iii. Could not induce vasogenic edema nor increase microhemorrhage, T- and B-cell infiltration, glial activation, and neuronal degeneration.

AV-1959R vaccine, along with other vaccines based on MultiTEP, stimulates adaptive immunity, providing broad coverage of human MHC polymorphisms and activating both naïve Th cells and pre-existing memory Th cells (49, 52) generated in response to conventional vaccines and/or infections with various pathogens during one's lifespan. These "non-self" anti-MultiTEP Th cells activate B cells specific to disease associated A β epitope and induce the production of therapeutically potent antibodies specific to A β protein in humans similar to that observed in animal models. Our published data and data presented in the Investigator Brochure (36) supported this mechanism of action and demonstrated that the AV-1959R vaccine based on this platform is highly immunogenic in mice (1, 2), in rabbits, and macaques.

1.6 Proposed doses and immunization schedule

This protocol proposes a Phase 1 study design consisting of 2 sequential cohorts administrated with ascending doses of adjuvanted AV-1959R/A of 100 µg and 300 µg.

The 16 participants enrolled at a single site will be randomly assigned in 3:1 allocation to receive either active (AV- 1959R) or placebo (normal saline solution), both formulated with Advax-CpG55.2 [Advax- 15 mg and CpG-0.15 mg] via IM injections on Week 0 (Day 1), Week 4 (Day 28 ± 2d) and Week 14 (Day 98 ± 5d) and will be followed up for up to 8 weeks after last dose of IP.

Importantly, safety data generated with AV-1959R vaccine in 5XFAD transgenic mice mouse models, rabbits, and monkeys indicated that 100µg (mice, ~2500 µg/kg) and 50, 100, and 300µg (rabbits, ~15-100 µg/kg) and 100µg (monkeys, ~15µg/kg) delivered IM had been safe and immunogenic after 5 immunizations. These doses are ~3-500 times higher than the highest dose of AV-1959R (300µg per immunization, on average 5 µg/kg) proposed in the Phase I study calculated on per kg basis. Two immunizations (within two-week interval) with an immunogenic dose of AV-1959R followed by 1-2 booster injections with the same dose have been shown to be sufficient for the generation of robust cellular immune responses in all vaccinated animals, such as transgenic mouse model, rabbits, and monkeys. The strongest Th cell immune responses specific to the MultiTEP vaccine platform are detected 7-10 days after three immunizations in peripheral blood mononuclear cells (PBMC) isolated from monkeys and splenocytes obtained from mice. These Th cells synthesize and secrete cytokines to stimulate activated anti-Aβ specific B cells, producing therapeutically potent antibodies on days 14-21 after the third/fourth vaccinations. These dynamic data of immune responses support the schedule of immunizations and blood collection to detect antibodies in the proposed study. At the same time, it is well known that the half- life of human IgG antibodies is about 15-30 days, depending on concentration. (77, 78, 79) Therefore, antibody titers will be monitored in vaccinated subjects during the entire study in order to better understanding of the boosting regimen for future trials.

In human clinical trials, a dose of up to 15 mg of Advax and up to 0.15 mg of CpG55.2 given twice 3 weeks apart in adult human subjects was found to be safe and well tolerated.(29, 30, 31, 80) (ClinicalTrials.gov: NCT04453852; NCT04944368; NCT05005559; NCT05175625; NCT05231590; NCT05285384; NCT05148871; NCT05542862; NCT05279456; NCT03945825; NCT03038776; NCT01951677).

2. Study Objectives

2.1 Primary Objective

The primary objective of this study is to determine the safety and tolerability of adjuvanted AV-1959R vaccine compared to placebo in healthy participants.

2.2 Secondary Objectives

The secondary objective is to evaluate the immunogenicity of the adjuvanted AV- 1959R vaccine by assessing the level of humoral immune responses (anti-A β antibody levels: IgM and IgG isotypes and IgG1, IgG2, IgG3, and IgG4 subclasses) in plasma.

3. Investigational Plan

3.1 Study Design

This is a Phase 1, randomized, double-blind, placebo-controlled, multiple dose-escalating trial consisting of 2 ascending dose cohorts in healthy male and female participants, 40-60 years of age.

Subjects will undergo Screening visits within 4 weeks (up to 28 days) prior to the administration of the investigational product (IP) as per [Table 1](#) to identify eligible participants. Screening procedures may be performed in two or more screening visits. MRI examination for determination of subject eligibility will be performed at the later stage of screening.

A total of sixteen (16) subjects will be enrolled into the study in one of two dose cohorts. Eligible participants will be randomly assigned in a 3:1 ratio to receive 3 IM injections of either AV-1959R or placebo both formulated with Advax-CpG55.2 adjuvant at baseline (Week 0), Weeks 4 and 14 and undergo follow-up visit at Week 22 ([Table 1](#)). Each cohort will contain up to 8 subjects; six (6) will be randomly assigned to receive AV-1959R and two (2) participants to receive a placebo.

The following doses will be administered at each immunization time point:

Cohort	Study Drug (Dose)	Number of subjects
Cohort 1:	AV-1959R (100 µg)	6
	Placebo	2
Cohort 2:	AV-1959R (300 µg)	6
	Placebo	2

A Safety Review Committee (SRC) will be established to review the study progress, provide oversight for the determination of the safety of dose escalation, and determine if it is appropriate to continue the study or modify the protocol. Should the SRC choose not to escalate to the next dose level, previous dose level may be repeated if deemed necessary.

DLT will be monitored during the entire study. The DLT is defined as a serious or severe clinically significant AE (CTCAE Grade 3 or higher) not resolving within 14 days after each immunization in the dosing cohort that may be considered by the Investigator to be related to the study drug.

For each dose level, dosing will be staggered such that 2 subjects will be dosed prior to the rest of the group. Initially, 2 subjects (one active and one placebo) in each Cohort will be dosed (Immunization #1, Day 0) in a randomization ratio of 3:1 (active to placebo) prior to the rest of the cohort. General tolerability to treatment will be monitored over 14 days following each immunization of AV-1959R or placebo by the Investigator. If the safety assessments (AEs, clinical laboratory test results, vital sign measurements, 12 lead ECG results, and physical examination) are acceptable based on the judgement

of the Investigator on Day 15 \pm 2 and Day 42 \pm 3, individual participants will receive Immunization # 2 (Day 28 \pm 2) and Immunization # 3 (Day 98 \pm 5), respectively as planned.

Investigator will determine whether the remaining 6 subjects (five active and one placebo) in the Cohort will be dosed after review of a minimum of 14 days safety assessments (AEs, clinical laboratory test results, vital sign measurements, 12 lead ECG results, and physical examination) following first immunization of AV-1959R or placebo in sentinel group.

Dose escalation decision will be made by SRC based upon review of adverse events (AEs), and all safety data from 14 days after the first immunization of all 8 participants in first cohort before escalation to the second dose cohort.

Dose escalation will be determined by the number of subjects experiencing DLT not resolving within 14 days after the first immunization per dosing cohort:

- If ≤ 1 participant experienced a DLT two weeks after the first immunization, then initiation of the second dose (300 μ g) cohort may proceed.
- If ≥ 2 participants experience DLT two weeks after the first immunization, then no further dose increase will occur.

Dose escalation will be suspended or stopped if any of the following occurs:

- Death from any cause other than events clearly unrelated to the study drug;
- Any CTCAE Grade 3 or higher adverse event that certainly, probably/likely or possibly related to the study drug and persists for more than two weeks;
- Any serious or severe clinically significant AE (CTCAE Grade 3 or higher) that certainly, probably/likely or possibly related to the study drug and occurs within 4 weeks after product administration;
- Any other event(s) that in the opinion of the Investigator should invoke suspension of further enrollment.

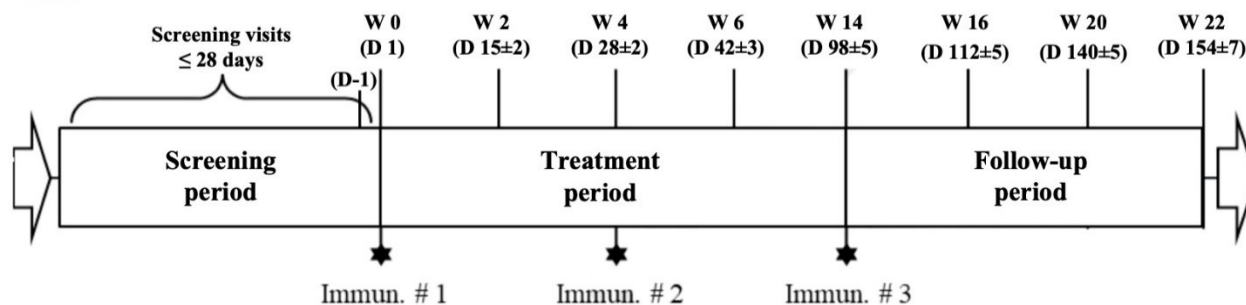
Based on safety information and number of DLT events, the SRC may decide to terminate the study at any time and the sponsor will submit appropriate reports to HREC and/or TGA.

Screening of new subjects may continue during SRC review meetings period between dose escalations. Safety and tolerability are assessed through AEs, physical examinations, vital signs, ECGs, laboratory assessments, and MRI examinations. A local screening MRI will be performed at screening as part of the study eligibility criteria and then at Week 22 for safety assessment. The MRI scans will be reviewed by the Investigator or qualified designee for immediate participant management.

Blood will be collected to measure anti-A β and anti-MultiTEP antibody titers prior to initiation of immunization (prior to 1st immunization) and at Weeks 6, 14 (prior to last immunization), 16, 20, and 22.

The overall study schematic is presented in [Figure 2](#) below:

Figure 2. Study design scheme.



4. Study Population

4.1 Number of Subjects

Up to 16 eligible healthy male or female of 40 to 60 years of age will be enrolled in this study.

4.2 Selection of Study Population

The Investigator will be responsible for confirming subject eligibility by documenting in the electronic case report form (eCRF) that each subject meets all of the inclusion criteria in [Section 4.2.1](#) and does not meet any of the exclusion criteria in [Section 4.2.2](#).

Prior to any study-related activities, an ICF approved by the HREC must be signed and personally dated by the subject. The subject's original signed and dated ICF (together with any subsequent amended versions approved by the HREC) must be retained by the investigator in the subject's file. A copy of the original signed and dated ICF must be given to the subject.

4.2.1 Inclusion Criteria

A subject must meet all of the following inclusion criteria to participate in this study:

1. Healthy, adult, male or female of non-childbearing potential, 40 to 60 years of age, inclusive, at Screening visit.
2. Body mass index (BMI) ≥ 18.0 and ≤ 32.0 kg/m² at Screening visit
3. Medically healthy with no clinically significant medical history, abnormalities in physical examination, laboratory variables, vital signs, ECG or MRI at the time of Screening and Baseline (if applicable), as deemed by the Investigator or designee.
4. Signed informed consent form by the participant prior to initiation of any study-related procedures.
5. If female of non-childbearing potential, must meet at least one of the following criteria:
 - a. post-menopausal status defined as amenorrhea for at least 12 months prior to study drug dosing in absence of any exogenous hormonal treatments and follicle stimulating hormone (FSH) levels in the laboratory defined post-menopausal range.
 - b. subject report of surgical sterilization (i.e., hysterectomy, bilateral tubal ligation, bilateral oophorectomy/ salpingectomy) at least 6 weeks prior to Day 1. Documented evidence of surgical sterilization is required.

6. If male, must have had a vasectomy 90 days prior to the Screening visit with a follow up negative sperm count, or agree to not donate sperm for 90 days after the last dose of study drug and, if engaging in vaginal sexual intercourse with a female partner of childbearing potential, agree to use a condom in addition to the female partner must use a highly effective method of birth control (e.g. intrauterine device, diaphragm, hormonal contraceptives) throughout the duration of the study treatment period and for 90 days after the last dose of study drug. Abstinence from heterosexual intercourse is an acceptable method of contraception. Subjects with same-sex partners (abstinence from penile-vaginal intercourse) are eligible without needing contraception when this is their usual form of sexual relations.
7. Ability, in the opinion of the investigator, to understand the nature of the trial and comply with protocol requirements, including the prescribed dosage regimens, scheduled visits, laboratory tests, and other trial procedures.

4.2.2 Exclusion Criteria

A subject will be excluded from participation in this study if he or she meets any of the following criteria:

1. Any clinically significant medical history or observations at the time of Screening visit not specifically excluded in other criteria that, in the opinion of the Investigator or designee, may confound the results of the study, compromise the safety of the subject or otherwise render the subject unsuitable for participation.
2. Magnetic resonance imaging (MRI) showing evidence of any of the following at the Screening:
 - 1 or more small non-cortical lacunar infarct greater than 1.0 cm
 - Any territorial infarct including acute or chronic
 - Subjects who have microbleeds and areas of leptomeningeal hemosiderosis
 - Subjects who have a presence of any other significant cerebral abnormalities, including ARIA-E, as assessed in the screening MRI scan.
3. Contraindications for MRI scanning, including implanted metallic devices (e.g., non-MRI-safe cardiac pacemaker or neurostimulator; some artificial joints metal pins; surgical clips; or other implanted metal parts), or claustrophobia or discomfort in confined spaces.
4. Any serious illness requiring systemic treatment and/or hospitalization within 4 weeks prior to study entry.

5. History/evidence of clinically relevant pathology related to the cardiovascular system, respiratory tract, gastrointestinal tract, endocrinology, immunology, hematology, or any other systemic disorder/major surgeries that, in the opinion of the Investigator, would confound participation and follow-up.
6. History or presence of any of the following:
 - clinically significant acute illness or surgery within the previous 3 months of Day 1.
 - hypersensitivity reaction or anaphylaxis to any medication to be of clinical significance to the current study or compromise the safety of the subject in the opinion of the Investigator
 - history or suspicion of routine or chronic drug or alcohol abuse or dependence within 1 year prior to Day 1 based on subject report; excessive alcohol intake (defined as routine weekly intake of greater than 21 glasses/units per week, with one unit=150 mL of wine or 360 mL of beer or 45 mL of 45% alcohol).
7. Clinically significant laboratory abnormalities at Screening visit, including (but not limited to):
 - hemoglobin, hematocrit, total white blood count (WBC) or platelet count below the lower limit of the normal range
 - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >1.5 times the upper limit of the normal range
 - serum creatinine above the upper limit of the normal range or estimated creatinine clearance <90 mL/minute as calculated by the Cockcroft-Gault equation
 - positive testing for human immunodeficiency virus (HIV-1 or -2), hepatitis B surface antigen (HBsAg), or positive testing for hepatitis C (HCV)

Clinical laboratory tests may be repeated as per Investigator's discretion.

8. Systolic blood pressure (BP) >160 millimeters of mercury (mmHg), or <90 mmHg; diastolic BP >95 mmHg or <50 mmHg blood at Screening visit or Day 1. Vital signs may be repeated as per Investigator's judgement.
9. Supine heart rate less than 45 beats per minute (bpm) or higher than 100 bpm at the Screening visit or Day 1. Vital signs may be repeated as per Investigator's judgement.
10. ECG with QTcF interval duration equal or greater than 450 msec for males and 470 msec for females obtained after at least 5 minutes in a supine or semi-recumbent position at quiet rest at Screening visit or Day 1.

11. Any other medical, psychological, or social condition that, in the opinion of the Investigator, would prevent the participant from fully participating in the study would represent a concern for study compliance or would constitute a safety concern to the participant.
12. Participation in another investigational drug study or treatment with an investigational drug within 30 days or 5 half-lives, whichever is longer, before dosing.
13. Prior administration of any tau or amyloid-beta immunotherapy (vaccine, antibody) within 1 year prior to Screening.
14. The use of immunomodulatory or growth-stimulating factors such as systemic corticosteroids, cyclosporine, methotrexate, azathioprine, anti-CD25 antibody, GM-CSF, C-CSF, interferon (IFN), or interleukin-2 (IL-2) within 30 days prior to study entry.
15. Chronic use (>3 months) of warfarin, other coumarin derivatives, anticoagulants, or an anti-platelet agent (e.g., clopidogrel).
16. Parenteral use of immunoglobulin preparations, blood products, and plasma derivatives.
17. History/evidence of severe local or systemic reactions to vaccination or significant allergic reactions.
18. Female of childbearing potential.
19. Any skin condition and/or tattoo that may interfere with the evaluation of safety at the injection site.
20. Donation of blood or significant blood loss greater than 400 ml within the last 30 days prior to dosing.

4.3 Subject Disposition and Discontinuation

4.3.1 Duration of Study Participation

The maximum duration of participation for each subject will be approximately 26 weeks, including up to 4 weeks for screening, 14 weeks for treatment, and 8 weeks follow up period after the last dose of IP. The duration of study participation is defined for each subject as the date written informed consent is provided through the end of study (EOS) visit, which is up to 56±7 days post last dose or the date of early termination (ET) for subjects who are withdrawn prior to the end of study assessment.

4.3.2 Subjects Withdrawal and Discontinuation

Subjects will be informed that they are free to withdraw from the study at any time. The Investigator may exercise his or her medical judgment to terminate a subject's participation in the study due to

clinically significant changes in any clinical or laboratory parameters, or non-compliance with study procedures.

Sponsor also reserves the right to terminate the study at any time for any reason. All data normally collected at completion of the study will be collected either at the time of the subject's early termination, or on or before the scheduled study visit.

Study drug administration or a subject's participation in this trial may be discontinued for any of the following reasons at the discretion of the Investigator:

- If the subject withdraws his/her consent for any reason.
- If the subject's condition has worsened to the degree that the Investigator feels it is unsafe for the subject to continue in the study.
- If the subject has poor venous access making it difficult/impossible to obtain laboratory samples.
- If an adverse event (AE) occurs for which the subject desires to discontinue treatment or the Investigator determines that it is in the subject's best interest to be discontinued.
- If there is a major protocol deviation or a trend in major deviations.
- If a concomitant therapy is reported or required which is likely to interfere with the results of the study or compromise subject safety.
- If the subject is lost to follow-up. The Investigator will document efforts to reach the subject at least twice by telephone and by a certified follow-up letter before determining that the subject is lost to follow-up.
- If a subject becomes pregnant. If a subject pregnancy is reported during study participation, the pregnancy will be followed until the outcome of the pregnancy and the resulting child will be followed for 1 year post birth.
- Administrative reasons.
- Other. *Note: This category includes withdrawals caused by an accidental or a medical emergency, unblinding, or other rare cases. This also includes withdrawal due to medical, psychological, or social condition which, in the opinion of the Investigator would prevent the subject from fully participating in the study, would represent a concern for study compliance, or would constitute a safety concern to the subject. The specific reasons will be recorded on the eCRF.*

The clinical report will include reason(s) for subject withdrawals as well as details relevant to the subject withdrawal.

4.3.3 Handling of Withdrawals

The Investigator may terminate a subject's study participation at any time during the study if the subject meets the withdrawal criteria described in [Section 4.3.2](#). In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary reason for termination must be recorded. If a subject is discontinued from the study for any reason, efforts should be made to perform final assessments outlined for the Day 154 (± 7 d) follow up visit if deemed safe by the Investigator.

In the event that a subject discontinues from the study at any time due to an AE, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. In this case, the Investigator must follow the subject until the AE has resolved, becomes clinically insignificant, or is stabilized, unless the subject is lost to follow-up.

4.3.4 Replacement of Subjects

Subjects who withdraw or are withdrawn for non-safety reasons during the study drug treatment may be replaced on a case-by-case basis per Sponsor's discretion.

4.3.5 Screen Failures

Any subject who sign the ICF and is deemed ineligible to participate in the study or eligible subjects who are not randomized (due to completion of enrollment or backup subjects) will be considered as screen failure. Subjects who do not qualify based on a reversible condition or mild intercurrent illness, in the opinion of the Investigator, may be rescreened after the underlying condition is resolved.

4.4 Safety Review / Dose Escalation Committee

A Safety Review Committee (SRC) will provide study oversight for the determination of the safety of dose escalation. The SRC will include the sponsor's medical monitor, independent medical monitor and the PI, additional experts may be included in the SRC but will not be voting members. Details of SRC responsibilities, membership, procedures, and documentation will be specified in SRC charter.

The SRC will be informed of all deaths, serious unexpected adverse events, and all serious adverse events immediately after the Sponsor has been notified. The chair of the SRC will receive a report of an event as soon as the Sponsor receives the report from the Investigator. The report will then be reviewed by the full SRC.

4.5 Dose Escalation Rules

Dose-limiting toxicity (DLT) will be monitored during the entire study. The DLT is defined as a serious or severe clinically significant AE (CTCAE Grade 3 or higher) not resolving within 14 days after each immunization in the dosing cohort that may be considered by the Investigator to be related to the study drug.

For each dose level, dosing will be staggered such that 2 subjects will be dosed prior to the rest of the group. Initially, 2 subjects (one active and one placebo) in each Cohort will be dosed (Immunization #1, Day 0) prior to the rest of the cohort. General tolerability to treatment will be monitored over 14 days following each immunization of AV-1959R or placebo by the Investigator. If the safety assessments (AEs, clinical laboratory test results, vital sign measurements, 12 lead ECG results, and physical examination) are acceptable based on the judgement of the Investigator on Day 15 \pm 1 and Day 42 \pm 3, individual participants will receive Immunization # 2 (Day 28 \pm 2) and Immunization # 3 (Day 98 \pm 5), respectively as planned.

Investigator will also determine whether the remaining 6 subjects (five active and one placebo) in the Cohort will be dosed after review of a minimum of 14 days safety assessments (AEs, clinical laboratory test results, vital sign measurements, 12 lead ECG results, and physical examination) following first immunization of AV-1959R or placebo in sentinel group.

Dose escalation decision will be made by SRC based upon review of AEs, and all safety data from 14 days after the first immunization of all 8 participants in first cohort before escalation to the second dose cohort.

Dose escalation will be determined by the number of subjects experiencing DLT not resolving within 14 days after first immunization:

- If ≤ 1 participant experienced a DLT two weeks after the first immunization, then initiation of the second dose (300 μ g) cohort may proceed.
- If ≥ 2 participants experience DLT in two weeks after the first immunization, then no further dose increase will occur.

4.6 Stopping Rules

When an investigator identifies an event potentially associated with a stopping rule noted below, the Investigator must notify Sponsor Medical Monitor (MM) immediately. MM will then notify the SRC. The SRC will determine if any of the following stopping rules shall be invoked:

- Death from any cause other than events clearly unrelated to the study drug;
- Any CTCAE Grade 3 or higher adverse event that certainly, probably/likely or possibly related to the study drug and persists for more than two weeks;
- Any serious or severe clinically significant AE (CTCAE Grade 3 or higher) that certainly, probably/likely or possibly related to the study drug and occurs within 4 weeks after product administration;
- Any other event(s) that in the opinion of the Investigator should invoke suspension of further enrollment.

The Sponsor has the right to terminate the study at any time in case of safety concerns or it becomes unjustifiable for medical or ethical reasons to continue the study. In addition, termination or modification may be recommended for any other perceived safety concern based on clinical judgment, including but not limited to a higher than anticipated rate for any component of the primary endpoint, device failures resulting in adverse events, or unexpected SAEs.

5. Study Treatments

5.1 Investigational Product

5.1.1 Identity of Study Drugs Used in the Study

The AV-1959R drug product is clear to slightly opalescent, colorless to slightly yellow solution. AV-1959R will be supplied in vials containing a drug product formulated to the final protein concentration of 1.1mg/mL. The fill volume target is about 0.7mL.

Placebo will be prepared by the pharmacy by mixing Advax, CpG and normal saline solution, and will not contain a drug product.

AV-1959R and Placebo formulations are manufactured, tested, and released according to Good Manufacturing Practices.

Advax and CpG55.2 are supplied separately as preservative-free suspensions in phosphate buffered saline in glass vials that contain:

- Advax vial - 0.5 mL at 50mg/mL, total content 25 mg
- CpG55.2 vial - 0.5 mL at 2 mg/ml, total content 1 mg

5.1.2 Formulation, Packaging, and Labeling

AV-1959R and Placebo will be packaged by Sponsor or sponsor-approved vendor and supplied in single-dose vials. All labeling and packaging will be the responsibility of the Sponsor and will be performed according to GMP and the local regulatory requirements.

The Advax and CpG55.2 adjuvant is presented as two separate vials, one containing delta inulin and the other containing CpG55.2 which need to be mixed together before use.

The AV-1959R and adjuvant component(s) are diluted with natural saline solution, drawn up into separate syringes, via Fluid Dispensing Connector mixed in the new syringe for injection.

Further details of study drug preparation will be provided in the Pharmacy Manual for the study.

5.1.3 Storage and Handling of Investigational Product

Drug product AV-1959R and Placebo must be kept in a freezer at $\leq -60^{\circ}\text{C}$, while Advax and CpG55.2 adjuvants must be kept at $2-8^{\circ}\text{C}$ (Do not freeze) in a secure cabinet or room with access restricted to necessary study site personnel. Prior to using the AV-1959R vials should be thawed at $4-8^{\circ}\text{C}$. When completely thawed, the vials should be gently mixed, and formulation with Advax and CpG55.2 should be prepared and administered as described in a Pharmacy Manual.

The study drugs must be stored as labeled in a secure area with access limited to the authorized staff. The study drugs will be stored securely under the appropriate conditions according to local standard operating procedures. The Investigator has overall responsibility for ensuring that study drugs are stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacist or member of the study team, but this delegation must be documented.

The Sponsor will provide a sufficient quantity of study drugs supplies to the site. Upon receipt of the study medication, the Investigator or the responsible pharmacist will inspect the study drugs. All study drugs will be handled, reconstituted, prepared, labeled, dispensed, and accounted for according to the Pharmacy Manual.

The study medication will be kept in the pharmacy or in a locked and secured storage room at the site accessible only to those authorized by the Investigator to dispense the study medication. The personnel responsible for study drug will keep an inventory of unused and used vials. This will include a description of the formulation and the quantity of investigational materials received for the study and a record of the materials that are dispensed.

5.1.4 Investigational Product Accountability

In accordance with the Code of Federal Regulations (21 CFR 312.62), the Investigator is required to keep accurate records showing the final disposition of all study drugs.

The Investigator and/or delegated pharmacist will maintain records of the product delivery at the site, the inventory at the site, the use by each subject, the return to the Sponsor or alternative disposition of unused products. These records will include dates, quantities, batch numbers, expiry date, and the unique code numbers assigned to the IP and study subject.

The Investigator must not use material provided for this particular study in another study without prior written approval from the Sponsor.

Adequate records of the receipt and disposition of all received IP are to be maintained at the site.

5.1.5 Disposal and Destruction

At the end of the study and once IP inventory accountability is completed, the Sponsor may authorize destruction of all used, partially used, and unused vials. If the site is capable of destroying designated study materials, it may do so only upon authorization by the Sponsor. Used vials of drug product, placebo, and Advax-CpG55.2 admixtures may be destroyed in accordance with site- specific SOPs

following each monitoring visit where study product accountability is monitored, and resolution of any discrepancies.

5.1.6 Method of Assigning Subjects to Treatment Groups

A statistician who will not be involved in the ongoing study will generate the randomization schedule. The randomization treatment assignment information will be secured and housed kept in a locked storage area, accessible only by the assigned unblinded pharmacist and his or her verifier.

Approximately 16 subjects will be randomly assigned to receive either AV-1959R or placebo treatment in a 3:1 ratio. Randomization is to occur on Day 1 before study drug administration.

Blinding information is provided in [Section 5.5](#).

5.2 Treatment Administered

The following treatments will be administered in each cohort:

Cohort	Study Drug (Dose)	Adjuvant	Number of subjects
Cohort 1:	AV-1959R (100 µg)	Advax-CpG55.2 [Advax-15mg, and CpG-0.15mg]	6
	Placebo	Advax-CpG55.2 [Advax-15mg, and CpG-0.15mg]	2
Cohort 2:	AV-1959R (300 µg)	Advax-CpG55.2 [Advax-15mg, and CpG-0.15mg]	6
	Placebo	Advax-CpG55.2 [Advax-15mg, and CpG-0.15mg]	2

Preparation of AV-1959R or Placebo with adjuvant: Vaccine formulation (AV-1959R or Placebo) should contain an appropriate dose of the AV-1959R (100 µg or 300 µg) or Placebo with adjuvant Advax-CpG55.2. Study vaccine preparation will be performed by the site's pharmacist or designee on the day of administration. Admixture of vaccine and adjuvants by the unblinded research pharmacist or designee must be performed under a laminar flow hood using an aseptic technique according to USP 797 guidelines and local institutional guidelines. Detailed instructions for vaccine preparation will be described in the Pharmacy Manual.

Treatment administration: AV-1959R vaccine or Placebo administration to the subject will be performed by a blinded study personnel member. Each dose of the study drug will be administered to the subject via a single IM injection into the deltoid muscle of the subject's preferred arm. The site of injection (right and left arms sequentially when possible) and time of study vaccine administration to the subject will be recorded on the appropriate source document. An aseptic technique will be used for the withdrawal and administration of each dose of the study vaccine using a disposable, sterile

needle appropriate in length for each subject. Details of dosing procedures will be provided in the Pharmacy Manual.

5.3 Treatment Compliance

All doses of the study drug will be administered at the site under direct observation of study personnel and recorded in the eCRF. Clinic personnel will confirm that the subject has received the entire dose of study drug.

5.4 Subject Numbering

Randomized subjects will be assigned unique subject numbers in sequential order based on their order of qualification.

5.5 Blinding

The study will be double-blind and a randomization schedule will be prepared by unblinded statistician. The randomization schedule will be secured within the pharmacy and only the unblinded pharmacist will have access to the randomization schedule.

Neither the subjects nor clinical staff administering or dispensing the study drug will know whether the subject is receiving active treatment or placebo. To maintain the blind, ready to be administered syringes with adjuvanted active AV-1959R and adjuvanted placebo normal saline solution without the active AV-1959R) will be prepared by the Pharmacy and delivered to the trial clinical site on the day of immunization.

5.5.1 Breaking the Blind

The investigator and site study personnel must remain blinded to the participant's treatment assignment. The blind should be broken only if the participant experiences a medical emergency and knowledge of the blinded treatment assignment is deemed necessary for further management of the participant. An emergency code break in a sealed envelope will be available to the PI and/or pharmacist.

If unblinding is deemed necessary for the safety of the participant, before breaking the blind, the investigator will attempt to contact the medical monitor to discuss the need for the unblinding. The investigator may break the blind independent of the medical monitor if the event is considered an emergency by the investigator and the code break is necessary for the management of the participant. The investigator must inform the medical monitor as soon as possible.

Individual code breaks by the investigator will result in withdrawal of the participant from the study. The date and reason for the code break must be documented in the source documents and on the appropriate electronic case report form (eCRF). The sponsor must be informed as soon as possible.

6. Study Procedures and Evaluations

6.1 Study Visits

Refer to the schedule of assessments ([Table 1](#)) for a summary of the schedule of study procedures. The duration of study participation for each subject is approximately up to 26 weeks.

6.1.1 Screening Period (Days -28 to -1)

The prospective subjects will visit the study center and be assessed by qualified properly educated, and instructed study staff.

Written information on the study and the associated risks will be provided to the subjects at the initial screening visit. Subjects must be allowed to read and understand the information provided and to prepare questions prior to being asked for consent. Subject must personally date and sign a written informed consent that has been approved by an HREC. No study-related procedures or activities will be performed until the subject is fully informed about the study and the consent form is properly signed and dated. The Investigator, or a qualified person designated by the Investigator, will explain the purpose and procedures of the study as well as potential benefits and risks and respond to any questions raised by the subject. Each subject will be given a copy of the fully signed and dated consent form.

The screening period will occur within 28 days prior to participant randomization on Day 1. Subjects will be instructed to return to the study site for additional visits as appropriate within the Screening period for completion of the required screening assessments. Extension of the Screening period beyond the 28-day window to allow completion of screening procedures may be permitted after discussion between the Investigator and the Medical Monitor on a case-by-case basis.

Screening procedures may be performed in two or more screening visits. MRI examination for determination of subject eligibility will be performed at the later stage of screening.

Other safety assessments may be repeated at each screening visit at the discretion of the Investigator or when indicated.

The following assessments/procedures will be performed during screening period:

- Informed consent;
- Demographics;
- Medical history;

- Collection of prior/concomitant medication information;
- Height, body weight measurement and BMI calculation;
- Physical examination;
- Recording of vital signs (heart rate, blood pressure, respiratory rate and body temperature);
- 12-lead ECG;
- Collection of blood and urine samples for clinical laboratory tests, including hematology, serum chemistry, coagulation, urinalysis, serology, pregnancy (all females), and FSH (postmenopausal females) tests.
- Alcohol and drug tests
- MRI Examination

Subjects who meet all eligibility criteria will be scheduled for Day -1 check-in visit.

6.1.2 Day -1 Visit

The following assessments/procedures will be performed on Day -1:

- Review of concomitant medications
- Clinical laboratory tests (biochemistry, hematology, coagulation and urinalysis) and pregnancy test (females)

Subject eligibility will be reassessed, and eligible subjects will remain confined to the study site from Day -1 till the completion of the scheduled study procedures on Day 1.

6.1.3 Day 1 - Immunization #1

Subjects who meet the eligibility criteria will be randomized into one of the treatment groups. Study medication will not be dispensed until all screening procedures have been completed, eligibility has been verified and the subject has been randomized.

The following assessments/procedures will be performed on Day 1:

Pre-dose:

- Subject eligibility will be reviewed to ensure the subject remains eligible for the study since screening.
- Update medical history as applicable since screening.
- Review of concomitant medications

- Symptom-driven physical examination
- Vital signs within 15 minutes before the immunization (pre-dose)
- 12-lead ECG within 30 minutes before the immunization (pre-dose)
- Alcohol and drug tests
- Blood collection for anti-A β and anti-MultiTEP antibodies

Study drug (Active or Placebo) will be administered – Immunization #1.

Post-dose:

- 12-lead ECG at 4 hours post-dose
- Recording of vital signs at 15 min, 1 hour, 2 hours and 4 hours post-dose
- Assessment of AEs.
- Injection site reaction assessment at 30 min, 1 hour, 2 hours and 4 hours post-dose

Subjects will be instructed to return to the study site on Day 15 ($\pm 2d$).

6.1.4 Day 15 (± 2)

The following assessments/procedures will be performed on Day 15 ($\pm 2d$):

- Symptom-driven physical examination
- 12-lead ECG
- Vital signs
- Clinical laboratory tests (biochemistry, hematology, coagulation and urinalysis)
- Review of concomitant medications
- Assessment of AEs.

Subjects will be instructed to return to the study site on Day 28 ($\pm 2d$).

6.1.5 Day 28 (± 2) – Immunization #2

The following assessments/procedures will be performed on Day 28 ($\pm 2d$):

Pre-dose:

- Review of concomitant medications
- Symptom-driven physical examination
- Vital signs within 15 minutes before the immunization (pre-dose)
- 12-lead ECG within 30 minutes before the immunization (pre-dose)
- Clinical laboratory tests (biochemistry, hematology, coagulation and urinalysis) and pregnancy test (females)

- Alcohol and drug tests

Study drug (Active or Placebo) will be administered – Immunization #2.

Post-dose:

- 12-lead ECG at 4 hours post-dose
- Recording of vital signs at 15 min, 1 hour, 2 hours and 4 hours post-dose
- Assessment of AEs.
- Injection site reaction assessment at 30 min, 1 hour, 2 hours and 4 hours post-dose

Subjects will be instructed to return to the study site on Day 42 (± 3 d).

6.1.6 Day 42 (± 3)

The following assessments/procedures will be performed on Day 42 (± 3 d):

- Complete physical examination
- 12-lead ECG
- Vital signs
- Clinical laboratory tests (biochemistry, hematology, coagulation and urinalysis)
- Blood collection for anti- A β and anti-MultiTEP antibodies
- Review of concomitant medications
- Assessment of AEs.

Subjects will be instructed to return to the study site on Day 98 (± 5 d).

6.1.7 Day 98 (± 5) – Immunization #3

The following assessments/procedures will be performed on Day 98 (± 5 d):

Pre-dose:

- Review of concomitant medications
- Symptom-directed physical examination
- Vital signs within 15 minutes before the immunization (pre-dose)
- 12-lead ECG within 30 minutes before the immunization (pre-dose)
- Clinical laboratory tests (biochemistry, hematology, coagulation and urinalysis) and pregnancy test (females)
- Alcohol and drug tests
- Blood collection for anti-A β and anti-MultiTEP antibodies

Study drug (Active or Placebo) will be administered – Immunization #3.Post-dose:

- 12-lead ECG at 4 hours post-dose
- Recording of vital signs at 15 min, 1 hour, 2 hours and 4 hours post-dose
- Assessment of AEs.
- Injection site reaction assessment at 30 min, 1 hour, 2 hours and 4 hours post-dose

Subjects will be instructed to return to the study site on Day 112 (± 5 d).

6.1.8 Day 112 (± 5)

The following assessments/procedures will be performed on Day 112 (± 5 d):

- 12-lead ECG
- Vital signs
- Clinical laboratory tests (biochemistry, hematology, coagulation and urinalysis)
- Blood collection for anti- A β and anti-MultiTEP antibodies
- Review of concomitant medications
- Assessment of AEs.

Subjects will be instructed to return to the study site on Day 140 (± 5 d).

6.1.9 Day 140 (± 5)

The following assessments/procedures will be performed on Day 140 (± 5 d):

- 12-lead ECG
- Vital signs
- Blood collection for anti-A β and anti-MultiTEP antibodies
- Review of concomitant medications
- Assessment of AEs.

Subjects will be instructed to return to the study site on Day 154 (± 7 d).

6.1.10 Day 154 (± 7) – End of Study / Early Termination (EOS/ET)

The following assessments/procedures will be performed on Day 154 (± 7 d):

- Weight
- Complete physical examination
- 12-lead ECG
- Vital signs

- Clinical laboratory tests (biochemistry, hematology, coagulation and urinalysis) and pregnancy test (females)
- Blood collection for anti-A β and anti-MultiTEP antibodies
- MRI examination
- Review of concomitant medications
- Assessment of AEs.

Should any subject withdraw or be withdrawn from the study, all the end-of-study evaluations scheduled for Day 154 (± 7 d) should be performed at the time of discontinuation, if deemed safe by the Investigator.

6.1.11 Unscheduled Visits

Unscheduled visits are allowed by investigator discretion for safety reasons, administrative reasons (e.g., re-supply of study medication or diaries), or to address subject concerns or questions about the study. The following procedures and evaluations may be conducted at this visit as per investigator discretion if needed:

- Collection of concomitant medication information since the last visit
- Physical examination
- Weight
- Recording of vital signs
- 12-lead ECG
- Clinical laboratory tests (biochemistry, hematology, coagulation and urinalysis) and pregnancy test (females)
- Blood collection for anti-A β and anti-MultiTEP antibodies
- MRI examination
- Assessment of AEs.

6.1.12 Phone Follow-Up Days 2, 29 (± 2) and 99 (± 5)

Subjects will be contacted via phone call, internet/web, or other acceptable means of communication and will be questioned for assessment of adverse events the next day after each IP dosing in the trial.

6.2 Study Procedures

6.2.1 Demographics, Medical/Surgical and Prior/Concomitant Medication History

Demographics will include date of birth, sex, ethnicity, and race as described by the subject. The medical/surgical history of the subject will be obtained at the Screening visit(s). Specific information will be recorded on the CRF relating to any prior or existing medical conditions/surgical procedures involving the following: infectious diseases (including viral infections, such as hepatitis or HIV), allergies, metabolic/endocrine/nutritional, hematopoietic, musculoskeletal, dermatologic, head, ears, eyes, nose, and throat (HEENT), breasts, respirator cardiovascular, gastrointestinal /hepatic, genitourinary/renal, neurological and psychiatric/psychosocial.

History of prior and concomitant medications will be recorded in the CRF at the Screening visit.

6.2.2 Body Height and Weight

Body height (centimeters) and weight (kilograms) will be measured. Height will be measured at the Screening only. The subject will wear lightweight clothing and no shoes during weighing.

The subject's BMI will be calculated at screening using metric units and rounded to one decimal place according to the following formula: $BMI = \text{weight (kg)} / \text{height (m)}^2$

6.2.3 Physical Examinations

Physical examinations will be performed at the time points specified in the schedule of assessments ([Table 1](#)).

Complete physical examination will include, at a minimum, examination of the following body systems: General Appearance, HEENT, Neck (incl Thyroid & Nodes), Cardiovascular, Respiratory, Gastrointestinal, Renal, Neurological, Musculoskeletal, Skin, Other and the neurological system examination (assessment of mental status, cranial nerves, visual fields, sensory, motor, gait, primitive reflexes and tendon reflexes). Symptom-driven physical and/or neurological examinations may be done at any time point during the trial at the investigator's discretion.

Any significant changes from baseline in physical examination findings will be recorded as AEs.

6.2.4 Vital Sign Measurements

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature [°C]) will be measured at the time points specified in the schedule of assessments ([Table 1](#)).

Blood pressure and heart rate will be measured after the subject has been supine for at least 5 minutes. Pre-dose vitals will be performed within 15 minutes before dosing. Post dose vitals can be performed within ± 15 minutes from the scheduled time points. When vital signs are scheduled at the same time point as blood sample collection, vital signs will be measured first. Any significant deviations from Baseline vital signs, which are deemed CS in the opinion of the Investigator, will be recorded as an AE.

6.2.5 12-Lead Electrocardiograms

The ECG will be measured after the subject has rested in a supine position for at least 5 min at the time points specified in the schedule of assessments ([Table 1](#)). Pre-dose ECG will be performed within 30 minutes before dosing. Post dose ECG can be performed within ± 30 minutes from the scheduled time points. Whether measurement is performed, date performed, results, and findings will be recorded in the eCRF. When a blood collection is scheduled concomitantly with an ECG, the ECG should be taken prior to the blood collection.

Each 12-lead ECG will be evaluated by an appropriately qualified physician at the study site. ECG data will be evaluated using the following categories:

- Normal
- Abnormal, not clinically significant (NCS)
- Abnormal, clinically significant (CS)

Post-dosing (from first dose) abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed. All ECG source documentation will be retained at the site.

6.2.6 Clinical Laboratory Tests

Subjects will be required to fast for at least 4 hours before the clinical laboratory tests. Blood for laboratory tests will be taken at specific timepoints detailed in the schedule of assessments ([Table 1](#)). The Investigator can order lab panels that contain additional laboratory tests beyond those listed below. The clinical laboratory tests listed below will be recorded in CRF.

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges supplied by the laboratory are used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The following laboratory evaluations will be performed:

- **Hematology:** Haematocrit, Haemoglobin, Mean Cell Haemoglobin (MCH), Mean Cell Volume (MCV), Mean Corpuscular Haemoglobin Concentration (MCHC), MPV, Platelets,

Red Cell Count, Red Cell Distrib. Width. White Cell Count, Basophils, Eosinophils, Lymphocytes, Monocytes and Neutrophils

- **Biochemistry:** Albumin, ALP, ALT, Anion Gap, AST, Bicarbonate, Bilirubin (total, direct & indirect), Calcium (adjusted), Calcium, Chloride, Creatinine, eGFR, GGT, Globulin, LD, Phosphorus, Potassium, Protein, Sodium, Urea and Uric Acid
- **Coagulation:** Prothrombin time, activated partial thromboplastin time and International Normalized Ratio (INR).
- **Urinalysis:** Bilirubin, Blood, Glucose, Ketones, Protein, Specific Gravity, leucocyte esterase, pH, nitrite and urobilinogen. Microscopy examination (identification of cells, casts and crystals) may be performed if the urinalysis is abnormal and /or at discretion of Investigator.
- **Serology:**
 - Hepatitis Screen: HBsAg, and HCV Ab tests will be performed only at Screening.
 - HIV Screen: Subjects will have blood tested for HIV 1/ HIV 2 at Screening. Only those subjects negative for the presence of antibodies will be allowed to enroll in the study. The results of the HIV Ab testing will be retained by the study site in a confidential manner.
- **Pregnancy** test will be performed for all females at timepoints detailed in the schedule of assessments (Table 1). Serum pregnancy test will be done at Screening, and urine tests at subsequent timepoints.
- **Follicle stimulating hormone (FSH)** test will be performed on postmenopausal females.
- **Drugs of Abuse/Alcohol:** Alcohol breath test (as per site procedures), Urine drug test including: Methamphetamine, Opiates, Cocaine, THC, Phencyclidine, Benzodiazepines, Barbiturates, Methadone, TCAs and Amphetamine

The Investigator or medically qualified designee must interpret the laboratory findings (i.e., determine the clinical significance of any abnormal values indicated) and sign and date the laboratory report. Any clinically relevant changes requiring treatment during the study must be reported as an adverse event.

Only authorized and qualified persons may collect biological samples from the subject. The date and time of sample collection is to be recorded. Sample collection and handling procedures for laboratory assessments will be performed according to the procedures designated by the clinical site or laboratory.

6.2.7 MRI Examination

Magnetic resonance imaging (MRI) will be used to detect any evidence of brain impairment. The MRI Scan will be performed at the Screening visit and at EOS or ET ([Table 1](#)). Further details on the technique, procedures and analyses will be provided separately.

6.2.8 Local Tolerability Assessment

Assessment of injection site should be performed at 30 min, 1 hour, 2 hours and 4 hours post-dose with a window period of ± 15 minutes, and more frequently, if deemed necessary by the investigator. Infusion site reactions will be recorded as AEs. If any visible adverse reaction is observed, a photograph of the same will be captured. Assessments of injection site on other days will be performed in subjects who have unresolved injection site AEs.

6.2.9 Documentation of Concomitant Medications

All medications and therapy will be recorded beginning from 28 days before administration of study drug through follow-up. Any therapy administered prior to informed consent will be recorded as prior medication and medication ongoing at the time of signing the ICF or administered after informed consent will be recorded as concomitant medication. Relevant information (i.e., name of medication, dose, unit, frequency of administration, dates, and reasons for use) will be recorded in the source documents and in the eCRF. All changes in medication will be noted. If the reason for medication use meets the definition of an AE, the AE will be recorded on the appropriate page of the eCRF and in the source documents for that subject.

List of prohibited and restricted medications prior to/ during this study is provided below:

6.2.10 Prohibited Medications

- Concurrent use of warfarin or other coumarin derivatives or a combination of acetylsalicylic acid and an anti-platelet agent (e.g., clopidogrel) are prohibited. Low dose of acetylsalicylic acid (≤ 81 mg per day) is allowed.
- The use of immunomodulatory or growth stimulating factors such as systemic corticosteroids, cyclosporine, methotrexate, azathioprine, anti-CD25 antibody, GM-CSF, C-CSF, interferon (IFN), or interleukin-2 (IL-2) within 30 days prior to study entry ([Section 14.1](#)).
- CNS-active drugs are generally prohibited.
- Parenteral immunoglobulin preparations, blood products, plasma derivatives are prohibited.

- Any tau or amyloid-beta immunotherapy (vaccine, antibody) is prohibited within 1 year prior to Screening.

6.2.11 Restricted Treatments and Medications

- Consumption of alcohol, nicotine, caffeine and xanthine containing products are restricted for 24 hours prior to each dosing.
- Participants are restricted from strenuous exercise for 24 hours prior to any blood collection for clinical laboratory testing.
- Vaccination (e.g., flu shot or COVID-19).
 - Postpone the injection of IP to allow a 2-week lag after other vaccination, but no more than 4 weeks of the scheduled injection date.
 - Other anti-coagulants (non-coumarin related) are restricted for the duration of the study.
 - *When appropriate, review the International normalized ratio (INR) level and adjust dosage according to the prescribing information.*
- Sedative hypnotics are restricted for the duration of the study.
 - *Will be allowed if, in the opinion of the Investigator, use does not affect cognition AND participants are currently treated with a stable regimen (defined as no change to the participant's medication intake pattern rather than adherence to the prescribed regimen) for at least 12 weeks prior to randomization.*
 - *If initiated during study, maintain a stable regimen (including in the 6 weeks prior to clinical evaluation).*
 - *If taken as needed, these must be held for 72 hours prior to cognitive assessments, MRI is performed (as applicable).*
- Selective serotonin re-uptake inhibitors (SSRIs, e.g., paroxetine, sertraline, citalopram, escitalopram), serotonin norepinephrine re- uptake inhibitors (SNRIs, e.g., venlafaxine, duloxetine), atypical antipsychotics, and low dose tricyclic antidepressants are restricted for the duration of the study..
 - *Will be allowed if, in the opinion of the Investigator, use does not represent an exclusionary condition AND provided participants are currently treated with a stable*

regimen for at least 12 weeks prior to randomization. If initiated during study, maintain a stable regimen in the 6 weeks prior to clinical evaluation.

7. Assessment and Management of Adverse Events

7.1 Adverse Events

An AE is defined (per International Council for Harmonisation [ICH] of Technical Requirements for Registration of Pharmaceuticals for Human Use E2A, ICH, E2A) as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example) symptom, or disease associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A TEAE is defined as an AE with an onset that occurred after receiving study drug through study discharge, or a continuing AE diagnosed before the date of first dose of study drug, which increased in severity after the start of dosing.

An adverse reaction is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there are reasons to conclude that the drug caused the event.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, “reasonable possibility” means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a study drug.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the Investigator’s Brochure or at the specificity or severity that has been observed with the study drug being tested; or, if an Investigator’s Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. “Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Any pre-existing conditions or signs and/or symptoms present in a participant prior to the start of the study (e.g., before informed consent) should be recorded as Medical/Surgical History. Any change in health status, which is reported after informed consent and up to the last study visit will be recorded

as an AE. At each study visit, the Investigator will assess whether any subjective AEs have occurred. A neutral question such as, “How have you been feeling since your last visit?” will be asked. Subjects may report AEs that occur at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented on the AE page of the eCRF, whether or not the Investigator concludes the event to be related to the study drug. The event term, start and stop date, and severity will be documented, along with the Investigator’s opinion of the causal relationship between the event and study drug administration (certain, probable/likely, possible, unlikely, not related, unknown). All AEs will be followed until resolution or until the Investigator judges that further follow-up is not necessary. Each AE will be graded for severity by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0). The severity of each AE and SAE recorded in the eCRF should be assigned to one the following criteria:

- **Mild:** The experience does not cause substantial discomfort, symptoms are well tolerated, and do not interrupt or hinder the subject’s daily activities; the experience resolves spontaneously and no treatment is required beyond administration of nonprescription medication.
- **Moderate:** The experience causes some discomfort, symptoms interfere with but do not interrupt the subject’s daily activities; the experience may require treatment with prescription medication.
- **Severe:** The experience substantially hinders or interrupts the subject’s daily activities; the subject may be incapacitated and require prolonged treatment with prescription medication.
- **Life-Threatening or Disabling:** An event that poses an immediate risk of death from the reaction as it occurred.
- **Death:** The event resulted in death.

It is the Investigator’s responsibility to assess the relationship between the study drug and the AE to determine if a reasonable causality exists. The degree of “relatedness” of the AE to the study drug will be described using the following scale:

Certain:	<ul style="list-style-type: none"> ● Event or laboratory test abnormality, with plausible time relationship to drug intake ● Cannot be explained by disease or other drugs ● Response to withdrawal plausible (pharmacologically, pathologically) ● Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) ● Re-challenge satisfactory, if necessary
Probable/Likely:	<ul style="list-style-type: none"> ● Event or laboratory test abnormality, with reasonable time relationship to drug intake ● Unlikely to be attributed to disease or other drugs ● Response to withdrawal clinically reasonable ● Re-challenge not required
Possible:	<ul style="list-style-type: none"> ● Event or laboratory test abnormality, with reasonable time relationship to drug intake ● Could also be explained by disease or other drugs ● Information on drug withdrawal may be lacking or unclear
Unlikely:	<ul style="list-style-type: none"> ● Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) ● Disease or other drugs provide plausible explanations
Not Related:	<ul style="list-style-type: none"> ● The event is either a predose event or is definitely due to causes separate from the administration of the study drug, i.e., <ul style="list-style-type: none"> – documented pre-existing condition – technical and manual procedural problems – concomitant medication – subject's clinical state
Unknown:	<ul style="list-style-type: none"> ● The event does not meet any of the above criteria, because of conflicting data and/or dubious or insufficient/poor evidence the event is not judged as related or not related

The type of follow-up (telephone or on-site visit) will depend on the severity of the event at study completion.

Action Taken

An AE might lead to treatment of the event or changes in regard to the study drug. The following actions might be taken:

- None
- Change in the study drug administration:
 - Drug withdrawn
 - Drug interrupted
 - Dose reduced
 - Dose increased
- Drug treatment required (a medication was prescribed or changed; this will be recorded on the Concomitant Medication section of the eCRF)
- Non-drug treatment required (a non-drug treatment was prescribed or changed)
- Hospitalization/prolongation of hospitalization
- Diagnostic or clinical test(s) conducted
- Subject discontinued from the study

Outcome Categories

An AE can have one of the following outcomes:

- Recovered without sequelae
- Recovered with sequelae
- Ongoing
- Unknown
- Fatal

Severity of all adverse events will be evaluated by the Investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0¹⁰⁶ and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA).

7.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (i.e., the subject was at risk of death from the event. “Life threatening” in the definition of “serious” refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect;
- Important medical events that do not result in death, are not life threatening or do not require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If an SAE occurs, based on the Investigator’s judgment, appropriate therapy will be administered. Subjects will then be monitored closely as appropriate.

7.3 Additional Points to Consider for Adverse Events

Diagnoses versus signs and symptoms:

- Each AE will be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms will NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) will be recorded as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiological fluctuation).
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), only the diagnosis will be reported as an AE.

Pre-existing conditions:

- Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and will NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication will be recorded as an AE. The Investigator will ensure that the AE term recorded captures the change in the condition (e.g., “worsening of...”).

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition will be captured as an AE.

Elective surgeries or procedures:

- Elective procedures preplanned or performed where there is no change in the subject’s medical condition will not be recorded as AEs but will be documented in the subject’s source documents.

Overdose: If a subject has received more than the required amount of study medication inadvertently, this will be considered an overdose.

- Cases of study drug overdose without manifested side effects are NOT considered AEs.
- Any instance of symptomatic overdose (suspected or confirmed) must be considered as a SAE and reported accordingly.

7.4 Local Tolerability Assessment

Injection site reactions will be recorded in the eCRF separately to AEs and assessed as per the FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007)

Table for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization

Erythema/Redness *	2.5 - 5 cm	5.1 - 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

7.5 Reporting of Serious Adverse Events

Serious AEs require immediate reporting to the Sponsor (or delegate) and the Medical Monitor within 24 hours of the Investigator's knowledge of the event, whether or not the Investigator believes that the experience is related to study drug.

An SAE Form must be completed, signed by the Investigator, and include at a minimum: the event term(s), a short description of the AE, the reason why the AE is categorized as serious, the Investigator's current opinion of the relationship between the experience and the study drug (causality assessment), as well as the subject's identification number, sex, age, and relevant medical history.

Additional information, as appropriate, can be sent to the Sponsor and Medical Monitor when it becomes available (e.g., copies of relevant subject records, autopsy reports, and other documents). A corresponding AE eCRF must also be completed.

The Sponsor is responsible for notifying the HREC in writing of any SAE. All SAEs are to be documented in the eCRF with the date of onset and resolution, frequency, determination of seriousness, severity, action taken, outcome, and relationship to study drug.

Any SAE, including death, occurring while the subject is receiving study drug irrespective of the Investigator's opinion regarding study drug relationship, will be reported. Within 24 hours, the Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax or email to the Sponsor (or delegate) and Medical Monitor.

Any SAEs that occur from the informed consent through the participant's last visit/ contact that come to the attention of the Investigator, and are thought to be related to study drug, will be reported to the Sponsor (or delegate) and the Medical Monitor.

7.6 Follow-up of Serious Adverse Events

All SARs will be followed until the outcome is known or the subject's condition has stabilized.

All follow-up information on SAEs is to be reported within 24 hours of receipt by the Investigator in the manner described previously.

All fatal or life-threatening Suspected Unexpected Serious Adverse Reactions (SUSAR) will immediately be reported by the investigator to the sponsor, with a follow-up detailed report when this information is not contained in the initial report; the sponsor will report the event to the TGA immediately, but no later than seven calendar days after being made aware of the event, with any follow up information submitted to the TGA within a further eight calendar days.

All other SUSARs should be reported by the sponsor to the TGA no later than 15 calendar days after being made aware of the event.

All significant safety issues (SSIs) requiring implementation of urgent safety measures (USMs) should be reported by the investigator to the sponsor, and then the sponsor will be report to the TGA and HREC within 24 hours (where possible) and in any case, no later than 72 hours of the measure being taken. SSIs that arise from analysis of overseas reports (relating to a clinical trial in Australia) should be reported to the TGA under the same timeframe.

Action with respect to safety that has been taken by an overseas regulatory authority (relevant to an ongoing clinical trial in Australia) must be reported to the TGA by the sponsor without undue delay and no later than 72 hours of the sponsor becoming aware of the action.

All other SSIs (e.g., suspension of the trial, early termination of trial for safety reasons) must be reported by the sponsor to the TGA without undue delay and no later than 15 calendar days of the sponsor becoming aware of the issue or suspension or early termination.

Sponsor will prepare an expedited report for the TGA based on information provided by Investigator, and copies will be distributed to the Investigator.

A register of all event reports assessed and classified is to be retained by the Investigator and reported to the trial sponsor annually and the HREC.

7.7 Subject Deaths

All deaths of subjects, regardless of cause, occurring within 30 days after subject termination from the study, and which are known to the Investigator will be reported on the appropriate page of the eCRF. Documentation of the subject's cause of death and a copy of the autopsy report, if any, will also be provided. Pharmacovigilance (contact details provided in [Section 7.4](#)) must be notified immediately by telephone of all subject deaths. Fax/email modes of communication must be utilized

in case of any difficulty with telephone lines; written follow-up must be received within 3 working days of initial notification.

Death will not be reported as an SAE, but as a clinical outcome. The cause of death on a source document, such as the death certificate or autopsy report, will be used as the event term for the SAE. For subjects in which concurrent AEs or SAEs are present at the time of death, such AEs or SAEs will be marked as resolved with the date of resolution entered as the date of death.

Only the SAE that caused the subject's death will be marked with an outcome of "Fatal."

8. Data Analysis and Statistical Methods

All data collected will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum). Demographic and baseline characteristics will be summarized overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who discontinue and reasons for discontinuation will be presented. Details of all statistical analyses will be described in a separate statistical analysis plan (SAP).

8.1 Study outcome measures

Primary Outcome Measures

- Number of participants with Treatment-Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs) [Time frame: Baseline up to Week 22].

Secondary Outcome Measures

- Number of participants with clinically significant changes in vital signs [Time Frame: Baseline up to Week 22].
- Number of participants with clinically significant changes in ECG results [Time Frame: Baseline up to Week 22].
- Number of participants with clinically significant changes in laboratory test [Time Frame: Baseline up to Week 22].
- Number of participants with clinically significant changes in physical examinations [Time frame: Screening up to Week 22].
- Immunological Outcomes:
 - Serum anti-A β and anti-MultiTEP antibodies concentrations [Time Frame: Baseline up to Week 22].

8.2 Adverse Events

Adverse events will be summarized by system organ class (SOC) and preferred term.

Summary tables for TEAEs will include numbers and percentages of subjects experiencing TEAEs by system organ class and preferred term. If a subject has more than 1 TEAE that codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject

has more than 1 TEAE within a system organ class category, the subject will be counted only once in that system organ class category. The following summary tables will be included for each treatment and overall: summary of TEAEs, relationship of TEAEs to study drug, severity of TEAEs, AEs leading to study drug discontinuation, and SAEs. Adverse events will be listed by subject and tabulated for each cohort as well as pooled across cohorts for each dose level of the components. Different pooled groups will be detailed in the study SAP.

Data listings will be provided for all AEs, AEs leading to study drug discontinuation, and SAEs.

8.3 Clinical Laboratory Tests

Clinical laboratory results and change from before dosing to the end of the study will be summarized for each treatment using descriptive statistics (sample size, mean, SD, minimum, median, and maximum) at each scheduled time point. Shift tables will be provided for hematology, serum chemistry, coagulation, and urinalysis values. Clinical laboratory values that are outside of the reference ranges will be flagged in the data listings as clinically significant (CS) or not clinically significant (NCS). All clinical laboratory data will be presented in data listings.

8.4 Vital Sign Measurements

Descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum) of each vital sign measurement will be tabulated for each treatment. Abnormal results of vital sign measurements will be flagged in the data listings as CS or NCS. All vital sign data will be listed in the data listings.

8.5 Safety 12-Lead Electrocardiograms

Descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum) of each safety 12-lead ECG measurement will be tabulated for each treatment. Abnormal results of 12-lead ECG measurements will be flagged in the data listings as CS or NCS. All safety 12-lead ECG data will be presented in the data listings.

8.6 Other Safety Data

The physical examination findings and concomitant medications will be presented in the data listings.

8.7 Sample Size

The sample size of 16 subjects has no formal statistical basis and was chosen pragmatically based on clinical considerations to provide sufficient data for the safety objectives of this study.

9. Study Compliance

The Investigator agrees that the study will be conducted according to the principles of the ICH E6 (R2) and this Clinical Protocol. The Investigator will conduct all aspects of this study in accordance with AU TGA regulations, the ICH E6 (R2) GCP, and applicable local, state, and federal laws.

9.1 Modification to Protocol

The Sponsor will document all material changes to the protocol in the form of an amendment. Each amendment will be signed by the authorized Sponsor representative and the Investigator and approved by the HREC before implementation.

9.2 Protocol Deviations

No deviations to the protocol are permitted, except in instances when an emergency occurs that requires a departure from the protocol for participant safety. The nature and reasons for all protocol deviations will be recorded and reported at the end of the study in the CSR.

A minor protocol deviation is any protocol deviation that does not significantly impact on the participants' safety or compromise the integrity of study data.

A major protocol deviation is a protocol deviation that may significantly impact the completeness, accuracy, and/or reliability of the key study data or that may significantly affect a participant's rights, safety, or wellbeing. Key study data is any data that relates to primary and key secondary endpoints or activities critical to ensure participant safety, privacy and rights.

Should a major protocol deviation occur, the Sponsor must be informed as soon as possible. Reporting of major protocol deviations to the HREC and in accordance with applicable regulatory authority mandates is a PI responsibility.

All protocol deviations and the reasons for the deviations will be documented by the PI or designated staff.

10. Data Handling, Management and Records Keeping

10.1 Data Management

The full details of data management activities including procedures for handling of eCRF, database set-up and management, data entry and verification, data validation, quality control of database, and documentation of the performed activities will be provided in the Data Management Plan. The database, data entry screens, and program will be designed in accordance with the clinical protocol.

AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be classified according to the WHO Drug dictionary.

10.2 Case Report Forms

Completed eCRFs are required for each subject enrolled in the study. The Investigator retains full responsibility for the accuracy and authenticity of all data entered into the eCRF. The completed dataset and their associated files are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized business representatives or appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

Clinical data will be entered into eCRFs directly from the source documents. All data must be entered in English. The eCRF will include password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Authorized trial site personnel designated by the Investigator will enter data into eCRF. Appropriate training and security measures will be completed with the Investigator and all authorized trial site personnel prior to the trial being initiated and any data being entered into the system for any study subject.

The eCRFs should always reflect the latest observations on the subjects participating in the trial. Therefore, the eCRFs should be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety evaluations. The Investigator must attest that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off the clinical data.

10.2.1 Query Process

The monitor will review the eCRFs and evaluate them for completeness and consistency. Each eCRF should be compared with the respective source documents to ensure that there are no discrepancies between all data. All entries, corrections, and alterations are to be made by the Investigator or designee. The monitor cannot enter data in the eCRFs. Once clinical data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture application.

The appropriate investigational personnel will answer the queries in the eCRF. This will be audit trailed by the electronic data capture application meaning that the name of investigational personnel, time, and date is logged.

10.2.2 Source Documents

All information collected during the study will be recorded in source documents. Direct entries on the eCRFs are not allowed. The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or clinical site that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the trial. They include, but are not limited to, laboratory notes, memoranda, material dispensing records, subject files, any electronic record etc.

The Investigator must provide source documents for each subject who signed the Subject Informed Consent for inspection by the monitor at each monitoring visit. All supportive documentation, such as laboratory or medical site records, should be clearly identified with Subject Number. In case subject source document are to be shared with Sponsor or its designee, any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

10.2.3 User ID

eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of

the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction should be made in accordance with the relevant software procedures.

10.2.4 Audit trail

All changes will be fully recorded in a protected audit trail, and a reason for the change will be required. Once all data has been entered, verified, and validated, the database will be locked.

10.2.5 Management of Investigator Site File

Investigator Site File (ISF) will be managed and maintained by the Investigator. This will be the responsibility of the Investigator to keep the file updated and make the file available for review to study monitor, Sponsor designee, auditor or regulatory representative.

10.2.6 Records Retention at the Study Site

The Investigator agrees to keep the records and those documents that include (but are not limited to) the study-specific documents, identification log of all participating subjects, medical records, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), copies of all eCRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. All study records will be stored by the Sponsor for 15 years after the end of the study.

Refer to the Clinical Trials Research Agreement for the Sponsor's requirements on record retention. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

11. Quality Control and Quality Assurance

Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to Sponsor lies with the Investigator generating the data.

Before study initiation, Sponsor or designee will explain the protocol, IB, and eCRFs to the Investigator and study site personnel. In addition, the monitor will be available to explain applicable regulations and to answer any questions regarding the conduct of the study.

11.1 Good Clinical Practice

This study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Parts 50, 54, 56, 312 and 320)
- ICH E6 (R2)

11.2 Study Monitoring

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded in the eCRFs. Source documents are defined as original documents, data, and records. The Investigator and clinical site guarantee access to source documents by the Sponsor or its designee and by the HREC.

All aspects of the study and its documentation will be subject to review by the Sponsor or designee, including but not limited to the ISF, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the Investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

The details of the scope and frequency of monitoring will be provided in the Monitoring Plan.

11.3 Inspection of Records

The Investigator involved in the study will permit study-related monitoring, audits, HREC review, and regulatory inspection(s). In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, the competent authority, or other regulatory agency access to all study

records. The Investigator will promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

11.4 Quality Control

The clinical site shall implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the trial is being conducted and data are being generated, documented and reported in compliance with the protocol, GCP and applicable regulations. The Investigator may not deviate from the protocol without a formal protocol amendment having been implemented and approved by an appropriate HREC, except when necessary to eliminate immediate hazards to the subject or when the change involves only logistical or administrative aspects of the study.

The Investigator and Sponsor share the responsibility to ensure data quality and integrity. Training sessions, regular monitoring of investigation by Sponsor or designated personnel, instruction manuals, data verification, cross-checking and data audits will be performed to ensure quality of all study data. On-site site initiations will be performed to prepare Investigators and other study personnel for appropriate conduct of the study and collection of study data.

The Investigator will personally ensure the quality of the data by overseeing all study activities, including the timely review of both source data and eCRF data as transferred from source. The Investigator will sign and date a declaration attesting to his/her responsibility for the quality of all data recorded and stating that the data represents a complete and accurate record of each subject's participation in the study, and that it had been medically reviewed in a timely fashion throughout the data acquisition period.

Logic and consistency checks are to be performed on all data entered into the eCRFs to ensure accuracy and completeness.

11.5 Quality Assurance

At its discretion, Sponsor or Sponsor's designee may conduct audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the ICH harmonized tripartite guideline E6 (R2): GCP, the protocol, SOPs, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. The clinic site may also be compelled to undergo an inspection by a regulatory authority.

12. Human Research Ethics Committee Review

The Protocol and written ICF will be reviewed and approved by an HREC prior to any involvement of potential subjects. The composition of the HREC will be in accordance with the recommendations of the World Health Organization, ICH guidelines, and TGA regulations. If any member of the HREC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. If the US center is unwilling to provide names and titles of all members due to privacy and conflict of interest concerns, the center should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to HREC for the protocol's review and approval. This protocol, the IB or package insert, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to HREC for approval. Written approval by HREC of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (i.e., before shipment of the study drug). The HREC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date.

The Investigators will comply with all HREC reporting requirements. This may include notification to the HREC regarding: protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective HREC, and submission of the Investigator's final status report to HREC. All changes in research activities and all unanticipated problems involving risks to subjects will be immediately reported. No changes will be made in the conduct of the study without HREC approval, except when required to eliminate apparent immediate hazards to subjects. The HREC approval and relevant documentation for these items must be provided to the Sponsor or its designee.

12.1 Regulatory Approvals/Notifications

The study will be submitted by Sponsor or Sponsor designee to the TGA through CTN path. The study can be initiated at the site, once it has been approved by the responsible HREC.

12.2 Informed Consent

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki, the ICH Guidelines for GCP, and in accordance with all applicable laws and regulations. The ICF describes the planned and permitted uses, transfers and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF further explains the nature of the study, its objectives, and potential risks and benefits as well as the date informed consent are given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The ICF must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the Investigator to explain the detailed elements of the ICF to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the HREC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The current version of the HREC-approved consent form will be reviewed with the prospective study subject or his/her legal representative, and the investigator or his/her designee will answer questions regarding procedures, risks, and alternatives. The Investigator or his/her entitled designee (as defined on the Delegation List) will obtain written informed consent from each subject or from the subject's legal representative or designee. Written informed consent must be obtained before any study-specific procedure is performed. Documentation of the subject's informed consent for and participation in this study will be noted in the subject's medical record.

Once signed, the original ICF will be stored in ISF. A copy of the signed ICF shall be given to the subject.

All revised ICFs must be reviewed and signed in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record and the subject should receive a copy of the revised ICF.

12.3 Confidentiality of Subject Records

With respect to subject information collected in this study, the Investigator shall comply with the Privacy Act 1988. To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the

Sponsor requires that the Investigator permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., TGA), the Sponsor's designated auditors, and the appropriate HREC to review the subject's original medical records (source data or documents), including, but not limited to laboratory test result reports, ECG reports, admission and discharge summaries for clinical site admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

12.4 Delegation of Investigator Duties

The Investigator is responsible for personally conducting or supervising the study at the site. However, the Investigator is allowed to delegate certain study related tasks to sub-investigators and study staff. When tasks are delegated, the Investigator is responsible for providing adequate supervision and training of those to whom tasks are delegated.

12.5 Study Termination

Stopping rules for the study are specified in [Section 4.6](#). In addition, the study may be terminated if one of the following criteria is satisfied:

- New information regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the investigational medicinal product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

In general, the study may be discontinued for valid scientific or administrative reasons.

12.6 Financing, Insurance and Indemnification

Financing, insurance and indemnification shall be of a separate agreement(s) between the Investigator and Sponsor or its designee.

13. Ownership of Data and Publication Policy

Data derived from the trial are the exclusive property of Sponsor.

All publications associated with this study will be coordinated through the publication committee. The publication committee will consist of the Investigators, pharmacokineticist and representatives of the Sponsor. No publications will go forward without permission from the Sponsor. The Sponsor will provide the major findings of the study to the Investigators. At the Sponsor's request, the submission or other disclosure of a proposed publication will be delayed for up to 30 days to allow the Sponsor to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed publication. As a single center study, the first publication, or disclosure of study results shall be a complete report or disclosure coordinated by the Investigators and Sponsor. Thereafter, any secondary publications will reference the original publication(s). If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

14. Appendices

14.1 Appendix A: List of Immunomodulatory or Growth Stimulating Factors

The list below is not all-inclusive. The investigator must consult with Medical Monitor in case of other previous or concomitant immunomodulatory or growth stimulating factor medications.

Immunosuppressive or Immunomodulatory Drugs (generic names)

5-fluorouracil
Abatacept
Adalimumab
Altretamine
Anakinra
Azathioprine
Basiliximab
Belatacept
Bendamustine
Budesonide ≥ 6 mg
Busulfan
Carmustine
Certolizumab pegol
Chlorambucil
Cisplatin
Cyclophosphamide
Cyclosporine
Cytarabine
Daclizumab
Darvadstrocel
Diaziquone
Dimethyl fumarate
Etanercept
Everolimus
Fingolimod
Glatiramer
Golimumab
Hydrocortisone ≥ 80 mg
Hydroxychloroquine
Interferon beta-1a
Interferon beta-1b
Ixekizumab
Ifosfamide
Infliximab
Lomustine
Methotrexate

Melphalan
Mercaptopurine
Methotrexate
Methylprednisolon
e \geq 16 mg
Mycophenolate
mofetil
Natalizumab
Ocrelizumab
Ofatumumab
Oxaliplatin
Ozanimod
Prednisolone \geq 20 mg
Prednisone \geq 20 mg
Procarbazine
Rituximab
Ponesimod
Satralizumab
Secukinumab
Sirolimus
Siponimod
Streptozocin
Tacrolimus
Thalidomide
Temozolomide
Teriflunomide
Thioguanine
Thiotepa
Tocilizumab
Tofacitinib
Vedolizumab
Ustekinumab

Growth Stimulating Factors

Somatropin (Genotropin®, Humatrope®, Norditropin®, Saizen®, Serostim®, Flexpro®
Nutropin®, Nutropin AQ®, Omnitrope®, Skytrofa®, Sogroya®, Zomacton™, Zorbtive®)
Epoetin (Epogen® or Procrit®)
Darbepoetin alfa (Aranesp®)
Luspatercept (Reblozyl®)
Granulocyte colony stimulating factor (G-CSF, filgrastim, or Neupogen®)
Granulocyte macrophage-colony stimulating factor (GM-CSF, sargramostim, or Leukine)
Pegfilgrastim (Neulasta®)
Romiplostim (Nplate®)
Eltrombopag (Promacta®)
Oprelvekin (interleukin-11, IL-11, or Neumega®)

15. Revision History

Date:	Comment:
27 November 2023	Original Version 1.0
15 January 2024	<p>Version 2.0</p> <p><u>Rationale for the amendment:</u></p> <p>The protocol amendment was required to:</p> <ul style="list-style-type: none"> - Inclusion criterion #1 is amended to exclude female of childbearing potential and avoid potential risk for fetus and newborns. - Inclusion criterion #5 is removed in accordance with changes in criterion # 1 - Exclusion criterion #18: “Female of childbearing potential” is added. - Exclusion criterion #19: “Any skin condition and/or tattoo that may interfere with the evaluation of safety at the injection site” is added.
29 January 2024	<p>Version 3.0</p> <p><u>Rationale for the amendment:</u></p> <p>The broken link in the section 6.2.7 is restored.</p>
25 June 2024	<p>Version 4.0</p> <p><u>Rationale for the amendment - refer to Summary of changes from Protocol version 3.0 (January 29, 2024) to Protocol version 4.0 (June 25, 2024):</u></p> <p>The protocol amendment was required to:</p> <ul style="list-style-type: none"> - To further clarify participants dosing rule after safety assessment at post dose review period. - To further clarify dose escalation suspension/stopping rules. - To clarify documentation of sterilization for females with non-childbearing potential. - To clarify contraception requirement for males. - To correct inconsistency regarding subject position during vital signs measurement - To add new Exclusion criteria # 20 - To correct the placebo solution composition and the product preparation procedures. - To clarify alcohol and drug testing timepoint on Day 1 prior to dosing.

	<ul style="list-style-type: none">- To clarify specimen collection (Chemistry, Hematology, Coagulation and Urinalysis) on Day 28 (± 2) prior to dosing.- To correct inconsistencies regarding type and timing for conduct of physical examinations during the study.- To correct inconsistency regarding timing of adverse events recording during the study.- To correct discrepancies regarding allowable time window for the pre-dose vital measurements on Immunization Days.- To correct inconsistency regarding timing for weight measurement during the study. Weight measurement is not required on Day 1.- To correct inconsistency regarding timing for safety labs. Specimen collection (Chemistry, Hematology, Coagulation and Urinalysis) is not required on Day 140 (± 5).- To correct inconsistency regarding timing of serious adverse events recording during the study.- To correct typo regarding last measurable timepoint for the study outcome measures.- Other administrative changes and grammatical edits were made for consistency and accuracy throughout the protocol.
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