CLINICAL TRIAL PROTOCOL: NE3107-TRP-001

Study Title:	**A Phase II Open-Label Study for the Use of Anti-Inflammatory, Insulin-Sensitizing NE3107 for Treatment of Cognitive Decline Due to Degenerative Dementias**
Study Number:	NE3107-TRP-001
Study Phase:	2
Product Name:	NE3107 (17a-ethynyl-androst-5-ene-3b,7b,17b-triol)
IND Number:	159271
Indication:	Degenerative Dementias
Investigators:	Principal Investigator: **Dr. Sheldon E. Jordan, M.D., F.A.A.N.** Sub-Investigator: Dr. Bijan Pourat, M.D.

Sponsor:	The Regenesis Project
Sponsor Contact:	Sheldon Jordan, MD
Sponsor's Legal Representative:	Stephanie Berg, ND, JD 3019 Wilshire Blvd., #242 Santa Monica, CA 90403
Medical Monitor:	Sheldon Jordan, MD

Original Protocol:	11/04/2021
Amendment 1:	Version 2, dated 12/17/2021

SYNOPSIS

Sponsor: Sheldon Jordan MD Inc., dba The Regenesis Project

Name of Finished Product: NE3107

Name of Active Ingredient: 17a-ethynyl-androst-5-ene-3b,7b,17b-triol

Study Title: A Phase II Open-Label Study for the Use of Anti-Inflammatory, Insulin-Sensitizing NE3107 for Treatment of Cognitive Decline Due to Degenerative Dementias

Study Number: NE3107-TRP-001

Study Phase: 2

Primary Objective(s):
Primary endpoints will involve a comparison of neurophysiological health as evaluated by multi-modal brain MRIs obtained at baseline and post-intervention termination (3 months).

Secondary Objective(s):
Secondary endpoints will include a longitudinal comparison of cognitive functioning as well as serological inflammatory markers and glucose and insulin homeostasis.

Study Design:
The present open label study is designed to evaluate the potential efficacy of NE3107 among patients with degenerative dementias through neuroimaging, cognitive performance testing, and serological measures of insulin resistance.

Study Population:
Approximately 25 participants are planned to be enrolled in this study.

Diagnosis and Main Criteria for Inclusion
Inclusion criterion are a diagnosis of cognitive decline due to degenerative dementia and a clinical dementia rating (CDR) score of 0.5 or 1.

Test Product; Dose; and Mode of Administration:
NE3107 20mg BID

Duration of Treatment:
The duration of active intervention will be three (3) months.

Pharmacokinetic Variables:
The terminal plasma t1/2 for NE3107 is 6-8 hours. The estimated time to reach steady-state drug concentrations is 3 days using BID daily dosing.

Safety Assessments:
Safety and tolerability will be assessed using incidence reports, vital sign measurements, physical examinations, and clinical laboratory assessments.

Statistical Methods:
Statistical analyses will be run to compare change from baseline at the post-intervention termination follow-up (three months after baseline) using a level of significance of 0.05.

Date of Original Protocol: 4 November 2021

Date of Most Recent Protocol Amendment (if applicable): Version 2, dated 17 December 2021

Prepared in: Microsoft Word version 16

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LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
Aβ	Amyloid beta
Abin2	A20 binding inhibitor of NFκappaB activation 2
AChEI	Acetylcholine esterase inhibitor
AD	Alzheimer's disease
ADAS-Cog 11	Alzheimer's Disease assessment Scale-Cognitive Subscale 11
ADCOMS	Alzheimer's disease composite score
ADCS-CGIC	Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
API	Active pharmaceutical ingredient
ApoE(1-4)	Apolipoprotein E
APP	amyloid precursor protein
Arrestin	adaptor/scaffold proteins involved in inhibition of GPCR-mediated & intracellular signaling pathways
AUC	Time integrated drug exposure area under the curve
BACE1	beta secretase (cleaves APP)
BBB	Blood-brain barrier
BDNF	brain-derived neurotrophic factor
BID	twice daily
BMI	Body mass index
CCR2	C-C motif chemokine receptor 2 (binds MCP1)
CDR	Clinical Dementia Rating Scale
CHO	Chinese hamster ovarary (cell line)
C_{max}	Maximum concentration of drug in plasma or serum
CNS	Central nervous system
$cPLA_2$	phospholipase A2
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CXCL	C-X-C motif chemokine ligand
CYP	Cytochrome P450
EAE	experimental autoimmune encephalomyelitis
EC_{50}	half maximal effective concentration
ECG(EKG)	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ERK1, ERK2	extracellular signal regulated kinase 1 and 2
F(%)	Percent absolute oral bioavailability

Abbreviation	Definition
GABA	gamma amino butyric acid
GD	Gestation day
GDS-SF	Geriatric Depression Scale Short Form
GLP	Good laboratory practice
GRK	G protein-coupled receptor kinase
HbA1c	hemoglobin A1c
HDL	High-density lipoprotein
HE3129	3β,7β-dihydroxy-androst-5-en-17-one
HE3291	17α-ethynyl-androst-5-ene-3β,7α,17β-triol
HE3393	17α-ethynyl-3β,17β-dihydroxy-androst-5-en-7-one
HE3892	17α-ethynyl-androst-5-ene-2α,3β,7β,17β-tetrol
HE3545	17α-ethynyl-androst-5-ene-3α,7β,17β-triol
HE3633	17α-ethynyl-17β-hydroxy-androst-4,6-diene-3-one
hERG	Human-ether a-go-go related gene, K_v11.11 alpha subunit of potassium ion channel
HIS	Hachinski Ischemic Scale
HOMA	Homeostatic model assessment
HPA	hypothalamus-pituitary-adrenal
HPLC	High-performance liquid chromatography
Hsd17b4	17β-hydroxysteroid dehydrogenase 4
IFN	interferons
IκB	inhibitor of NFκB
IKK	IκB kinase
IL	interleukin cytokines
IGT	impaired glucose tolerance
IQGAP1	IQ Motif Containing GTPase Activating Protein 1 scaffold
IQR	inter-quartile range
IR	Insulin resistance
iv	intravenous
JNK	c-Jun N-terminal kinases
κB	promoter NFκB transcription site
KO	Knock out
KSR	kinase suppressor of Ras (scaffold)
LC-MS-MS	Liquid chromatography–tandem mass spectrometry
LDL	Low-density lipoprotein
LID	L-dopa induced dyskinesia
LPS	lipopolysaccharide
Lrp1	low density lipoprotein receptor related protein

Abbreviation	Definition
MEK	mitogen-activated protein kinase kinase (phosphorylates ERK)
MAP3K8	mitogen-activated kinase kinase kinase (phosphorylates MEK; Tpl2 in mouse, COT1 in human)
MAPK	mitogen-activated protein kinases
MAPK1	p42 ERK2
MAPK3	p44 ERK1
MCI	Mild cognitive impairment
MCP1	monocyte chemoattractant protein 1
mITT	Modified Intent-to-Treat
MPK1	mitogen-activated protein kinase phosphatase 1
MMP	matrix metallopeptidases
MMSE	Mini mental state exam
MNK	MAP kinase signal-integrating kinase
MP1	Mitogen-activated protein kinase scaffold protein 1
MORG	WD-repeat protein family scaffold
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSK	stress-activated protein kinase
MTD	Maximum tolerated dose
M value	mean glucose infusion rate
MW	Molecular weight
NE3107	17α-ethynyl-androst-5-ene-3β,7β,17β-triol
NOAEL	No-observed-adverse-effect-level
NEMO	NF-kappa-B essential modulator (aka IKKγ)
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NMT	Not more than
Nos	Nitric oxide synthase
NPI-12	Neuropsychiatric Inventory 12-Domain
p-	phospho substituent (e.g. p-ERK)
p38	p38 MAPK
p65	NFκB3
p105	NFκB subunit
Paxillin	scaffold encoded by the PXN gene
PBMC	Peripheral blood mononuclear cells
PD	Parkinson’s disease
PD98059	MEK inhibitor
PEA-15	proliferation and apoptosis adaptor protein-15

Abbreviation	Definition
PgP	P-glycoprotein
PK	pharmacokinetics
PK-PD	Pharmacokinetics-pharmacodynamics
po	Oral route of drug administration
PPAR	peroxisome proliferator activated receptors
QD	Once daily
QSAR	Quantitative structure-activity relationship
QT interval	Length of time from the start of the Q wave to the end of the T wave, the time taken for ventricular depolarization and repolarization
Raf	serine/threonine-specific protein kinases
Ras	small GTPase proteins involved in signal transduction
RAW264.7	mouse macrophage cell line
RH	Relative humidity
Rsp6ka3	p90 ribosomal S6 kinases
SAE	Severe adverse event
Sef	similar expression to fgf genes scaffold
SIRT2	sirtuin-2
SP1	specificity protein 1 (transcription factor)
$t_{1/2}$	Half-life
T2D	Type 2 diabetes
TG	Triglycerides
T_{max}	Length of time after drug administration to C_{max}
TLR	toll-like receptor
TNF	tumor necrosis factor
UC	Ulcerative colitis
ULN	Upper limit of normal
USP	United States Pharmacopeia
Vcam	vascular cell adhesion molecules
V_d	Volume of distribution

1 INTRODUCTION

Considering how many people are in a state of mild cognitive impairment (MCI) and frank dementia, there is a substantial cost to society in terms of financial burden and suffering (Connolly, 2018). Degenerative conditions that result in cognitive change in middle and late life are frequently associated with abnormal deposits of protein material (e.g., amyloid, phospho-tau) which interfere with neuronal function and viability (Lacor, Buniel, Furlow, Clemente, Velasco, Wood, et a., 2007; Khan, 2016). Inflammation and insulin resistance in the CNS and abnormal protein deposition and resultant physiological impairment characterize conditions of the Alzheimer's dementia (AD) type (Kinney, Bemiller, Murtishaw, Leisgang, Salazar & Lamb, 2018; Rorbach-Dolata & Piwowar, 2019).

Neuroinflammation prompts AD progression, impaired cholesterol efflux and reduced insulin signaling (insulin resistance) (Hølscher, 2020; Kinney et al., 2018; Rorbach-Dolata & Piwowar, 2019; Chow, Shi & Cheng, 2019. Insulin resistance has been considered a risk factor as well as a feature of AD, and has also been associated with increased aß-42 secretion, neuritic plaque burden, abnormal insulin receptor performance, decreased glucose metabolism, and consequently decreased cognitive performance (Holscher, 2020; Chow et al., 2019; Reading & Ahlem, 2021).

No therapy exists that has been proven to halt or reverse the progressive deposition of abnormal proteins or the attendant neurophysiological deterioration. Various investigational therapies aim to target the pathophysiological processes of AD; from combating abnormal protein deposition, to targeting sources of systemic and neuroinflammation, to providing cholinergic, hormonal, and metabolic support. A promising area of research is the ongoing use of insulin synthesizers as a therapeutic option for AD. Several Phase 3 studies have been initiated and/or completed with compounds such as Semaglutide, a hormone that stimulates insulin signaling (Nauck, Quast, Wefers, & Meier, 2020), Metformin, an insulin synthesizer (Koenig, Mechanic-Hamilton, Xie, Combs, Cappola, Xie, et al., 2017; Lin, Wang, Ma, Wang, Gong, Zhang, et al., 2018), and NE3107, an anti-inflammatory insulin-sensitizing agent (Reading & Ahlem, 2021).

In this study, the drug under investigation is NE3107 (17a-ethynyl0androst-5-ene-3b, 7b, 17b-triol). NE3107 is a small, blood-brain permeable molecule with anti-inflammatory and insulin-sensitizing properties. The mechanism of action for NE3107 involves selective inhibition of inflammatory mediators.

This study seeks to measure changes in advanced neuroimaging, CNS biomarkers of Alzheimer's disease, inflammatory serological and metabolic parameters, and cognitive performance measures among participants treated with NE3107.

The dose of NE3107 administered in this study will be 20 mg BID. Nonclinical safety studies and prior clinical trials have not identified a toxicity indicating the need for exploration of dose response. NE3107 dose response for anti-inflammatory and insulin sensitizing activity was not statistically resolved between 2, 5 and 10 mg BID in impaired glucose tolerance subjects in trial HE3286-0102. Neither preclinical data, nor available clinical information suggest an ordered dose response relationship across exposure on key indices of glycemic

control and insulin sensitivity. There has been no indication that NE3107's anti-inflammatory activity could be increased with higher exposures. The dose duration will be 3 months. The rationale for 3-month administration is to allow sufficient time for detectable change to occur. The route of administration for NE3107 will be orally. NE3107 is formulated with common excipients used in oral medications in #2 hard gelatin capsules. NE3107 capsules are stable at room temperature for at least 18 months.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

Primary endpoints will involve a comparison of neurophysiological health as evaluated by multi-modal brain MRIs obtained at baseline and post-intervention termination (3 months). Specifically, multi-modal MRI endpoints will include: (1) An increase or stabilization in glutathione levels (as measured by magnetic resonance spectroscopy, MRS) compared to baseline. Patients with cognitive decline often show characteristic change in MRS or volumetric evaluation compared to age-matched controls (Kuhn et al. 2021); (2) Stabilized and/or improved dendritic density compared to baseline (as measured by diffusion tensor imaging, DTI-NODDI); (3) Enhancement of arterial signal compared to baseline (as quantified by arterial spin labeling, ASL). Patients with cognitive decline often have decreased perfusion in temporal parietal or frontal regions of the brain with ASL perfusion (Kuhn et al. 2021); (4) increased functional connectivity of the nucleus basalis of Meynert (NBM) with both hippocampi as well as between both hippocampi compared to baseline, as visualized by seed analysis of blood-oxygen level dependent (BOLD) imaging as well as (5) increased neurovascular coupling as visualized by BOLD compared to baseline.

2.2 Secondary Objective(s)

Secondary endpoints will include a longitudinal comparison of metabolic and serological analysis (specifically measures of glucose and insulin homeostasis); the level of cognitive impairment as defined by neuropsychological testing. Neuropsychological testing measures will include the Quick Dementia Rating Scale (QDRS), Clinical Dementia Rating (CDR) score as estimated by the QDRS, the Alzheimer's Disease Assessment Scale (ADAS-Cog12), the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment (MoCA).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

The present study is designed as a Phase II, open-label study of patients with dementia to evaluate potential efficacy of NE3107 using serological measures of insulin resistance, cognitive performance testing, AD biomarkers, and neuroimaging endpoints. Baseline and outcome measures in this study utilize validated tests that are appropriate for repeated measures which are not affected by practice effects. Advantages of this study include the fact that the neuropsychological testing instruments and advanced MRI imaging protocols that have been in routine clinical deployment provide for a high degree of availability and reliability for diagnosis and for monitoring change of status. The study population is sufficiently broad and the conditions of interest are sufficiently prevalent so that recruitment of the projected numbers of participants is not a limiting factor.

The duration of treatment is 3 months. The rationale for 3-month administration is to allow sufficient time for detectable change to occur. To minimize risk, participants will be called within 24 hours following initiation of the drug and weekly thereafter, as well as attend monthly visits the principal investigator to evaluate for safety and tolerability of the study intervention. Mild, moderate, and severe adverse reactions will be reported on an ongoing basis. Previously observed adverse reactions are listed in Table 22 of the Investigator's Brochure. Participants will be discontinued if they have moderate or severe adverse reaction ratings according to the ICH SAE E2A.

(See Appendix 1, Study Events Table.)

3.2 Rationale for Study Design and Control Group

The dose of NE3107 to be used in this study is 20 mg BID. Nonclinical safety studies and prior clinical trials have not identified a toxicity that supports the need for exploration of dose response. In vitro data indicate NE3107 is active at low nanomolar concentrations. NE3107 dose response for anti-inflammatory and insulin sensitizing activity was not statistically resolved between 2, 5 and 10 mg BID in impaired glucose tolerance subjects in trial HE3286-0102, and neither preclinical data, nor available clinical information suggest an ordered dose response relationship across exposure on key indices of glycemic control and insulin sensitivity. There has been no indication that NE3107's anti-inflammatory activity could be increased with higher exposures. NE3107 pharmacokinetics have high standard deviations for maximum serum concentration (C_{max}) and daily area under curve (AUC), which raise the concern for drug holiday or suboptimal trough plasma concentrations in participants with the lowest exposure. The dose of 20 mg BID is expected to increase the lowest expected C_{max} and AUC values to within 1 standard deviation below the average values for 10 mg BID, with trough values greater than 1 ng/mL.

3.3 Study Duration and Dates

The proposed participant recruitment start date will begin on 15 January 2022 and end on 31 January 2022. The recruitment period of 2 weeks, active treatment intervention period of 3 months, and final follow-up period of 2 weeks yields an expected 4-month study duration.

The actual overall study duration, start date and end date may vary depending on participant recruitment.

4 STUDY POPULATION SELECTION

4.1 Study Population

Number of Participants

Approximately 25 participants are expected to be enrolled in this Phase II trial to evaluate longitudinal findings from multimodal MRI among the population that is being studied.

Gender of Participants

The gender distribution for this study will aim for a ratio of 50:50 men to women. This is to ensure that both men and women benefit equally from any potential efficacy of NE3107 in treating dementia and that neither men nor women are disproportionately burdened by any tolerability issues. Women who are pregnant, who may become pregnant, or who are breastfeeding will not be included in the study.

Age of Participants

The ages for the participants in this study will range from 50-89 years old. This age range was selected based on the fact that degenerative conditions that result in cognitive change occur in middle and late life.

4.2 Inclusion Criteria

In order for a subject to be considered for this study, the following criterion is required:

- Diagnosis of cognitive decline due to degenerative dementia
- Age within range of 50-89 years old
- QDRS score ranging from 1.5-12.5, with a converted Clinical Dementia Rating (CDR) score of 0.5 (mild cognitive impairment) to 1(mild dementia)

The QDRS scale will be given to all patients; a cutoff range for QDRS scores has been specified as 1.5-12.5 to qualify patients with a clinical dementia score (CDR) of 0.5 to 1.

4.3 Exclusion Criteria

In order for a subject to be considered for this study, he/she may NOT have any of the following:

- Subjects with contraindications for lumbar puncture, such as bleeding abnormalities, use of anticoagulant medications, and local skin or spine abnormalities. *See Section 6.6.1 "Laboratory Parameters," page 26.*

- Subjects with contraindications to magnetic resonance imaging (MRI) acquisition, including patients with non MRI-compatible pacemakers, defibrillators, or other implanted electronic devices.
- Women who are pregnant, who may become pregnant, or who are breastfeeding
- Reversible causes of cognitive impairment that explains the clinical status entirely, such as hypothyroidism, depression
- Advanced stages of any terminal illness or any active cancer that requires chemotherapy
- History of breast cancer
- Women with child-bearing potential who are not willing to use a double-barrier birth control method
- Males not willing to use a double-barrier birth control method with female sex partners with child-bearing potential
- Individuals with hepatic impairment as defined by:
    - Alanine aminotransferase (ALT) lab values >3x the upper normal limit (UNL)
    - Aspartate aminotransferase (AST) lab values >3x UNL

      OR
    - History of clinically significant liver disease in the Principal Investigator's medical judgment
- Individuals with renal impairment as defined by Creatinine clearance (Cockcroft-Gault formula) of <45 mL/min.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Study Drug

NE3107 is an investigational orally bioavailable, blood-brain barrier permeable anti-inflammatory agent with a new mechanism of action targeting multiple mechanisms of pathology in Alzheimer's disease. NE3107 is an uncharged, low molecular weight molecule, poly-hydroxylated synthetic derivative of the C-19 adrenal steroid series. *In vitro* studies have been conducted to measure membrane transport, active efflux/P-gp interaction, hepatic stability, CYP inhibition, and CYP induction.

5.1.2 Placebo or Control

All participants will receive the study drug; this study will utilize no placebo group.

5.2 Treatment(s) Administered

The drug under investigation is NE3107 (17a-ethynyl-androst-5-ene-3b,7b,17b-triol). NE3107 is formulated with common excipients used in oral medications in #2 hard gelatin capsules. The capsules are designed for oral administration. The dose of NE3107 (Biovie, inc.) is 20 mg twice daily (BID) approximately 12 hours apart, for the duration of 3 months. Study drug will be dispensed and monitored by the Sponsor.

5.3 Selection and Timing of Dose for Each Participant

The dose of NE3107 (Biovie, inc.) is 20 mg twice daily (BID) approximately 12 hours apart. The dose will be stable for the duration of the study intervention, and will be the same for all participants.

5.4 Method of Assigning Participants to Treatment Groups

All participants will receive active study drug at the same dosage.

5.5 Blinding

No blinding procedures will be utilized.

5.6 Concomitant Therapy

Concomitant medications will be considered any therapies that the patient begins/continues taking from the time point of 30 days prior to first dose of NE3107. Concomitant medications will be stabilized for 30 days prior to entry in the study protocol. There are no pharmacologically or toxicologically important NE3107 metabolites for consideration in drug exposure rationale, but memantine and acetylcholine esterase inhibitors, galantamine, donepezil and rivastigmine, are permitted as co-medications in the proposed study. Memantine and rivastigmine do not have appreciable interactions with hepatic CYP

enzymes, so they do not factor into drug-drug PK interactions. Donepezil is predominately metabolized by CYP2D6, but is also metabolized by CYP3A4. NE3107 is also metabolized primarily by CYP3A4. In conclusion, no drug-drug PK interactions with co-medications memantine, donepezil, galantamine and rivastigmine are expected with the proposed dose of 20 mg BID. As noted in the exclusion criteria, patients with contraindications for lumbar puncture (such as bleeding abnormalities requiring the use of anticoagulant medications) will not be permitted into the study. Additionally, participants with any active cancer requiring chemotherapy will not be permitted to take part in the study.

5.7 Restrictions

5.7.1 Prior Therapy

There are no restrictions of entry to the study based on prior therapy.

5.7.2 Fluid and Food Intake

Patients will be required to obtain bloodwork having fasted for a period of time no less than 8 hours. There are no other fluid or food intake restrictions during the course of the study.

5.7.3 Participant Activity Restrictions

The participant will have no activity restrictions related to study involvement.

5.8 Treatment Compliance

Participants / primary caregiver / study partner will be instructed to bring their unused investigational product (IP) to every visit. Compliance will be assessed by capsule counts. Details will be recorded in the case report form. All unused IP will be collected from the participant at V10/ET. Noncompliance is defined as taking less than 80% or more than 120% of the assigned dose during any outpatient evaluation period (visit to visit). Discontinuation for noncompliance is at the Investigator's discretion.

5.9 Packaging and Labeling

Each investigational study drug will be labeled (in English) with a statement indicating that the drug is an investigational drug to be used only by a Qualified Investigator and will include but not limited to: Drug Name, Strength, Protocol Number, Sponsor's Name and Address, the recommended storage conditions for the drug, Expiry/Retest Date (when available) and Lot/Batch Number.

5.10 Storage and Accountability

Records will be made of receipt and dispensing of NE3107 supplied. It is the responsibility of the Sponsor to ensure that storage of study drug is within guidelines of the Investigator's Brochure. It is the responsibility of the Manufacturer to ensure that all drug supplies provided for the study are manufactured under current Good Manufacturing Practices (cGMP) and are suitable for human use.

5.11 Investigational Product Retention at Study Site

Upon completion or termination of the study, all remaining study supplies will be retained according to applicable regulations. Once the retention period has elapsed, any remaining unused drug will be returned to the Manufacturer in the original containers, or destroyed, as directed in writing by the Manufacturer.

6 STUDY PROCEDURES

For this Phase II open label study, all participants will be screened following acquisition of a signed, written informed consent form.

Screening will involve confirmation that all inclusion criteria and none of the exclusion criterion are met. Following confirmation of inclusion and exclusion criterion, participants will undergo baseline testing to include the following: Advanced magnetic resonance imaging (MRI) of the brain, lumbar puncture, APoE genotyping, cognitive testing, and serological analysis.

All patients will have an advanced MRI of the brain to include T1 and T2-weighted structural images, susceptibility-weighted imaging, neuromelanin, arterial spin labeling (ASL) perfusion, blood oxygen level-dependent (BOLD) at rest, diffusion tensor imaging with neurite orientation density and dispersion (DTI-NODDI), and magnetic resonance spectroscopy (MRS) of the precuneus. MRI will demonstrate if patients have tumors, hydrocephalus, subdural hematomas and other structural etiologies of cognitive decline. Having the scan completed will be required for inclusion, but no specific imaging parameters will determine inclusion. The advanced MRI of the brain will be repeated upon completion of the 3-month study intervention period.

All patients will have APoE swab testing and a lumbar puncture for Aß42 and Tau proteins for Alzheimer's Spectrum. This spinal fluid examination has been shown to be both sensitive and specific for Alzheimer's disease. Cerebrospinal fluid (CSF) studies have demonstrated good sensitivity and specificity for mild cognitive impairment (MCI) and dementia of the Alzheimer's type. MRI volumetrics, perfusion scans and MR spectroscopy have shown to be responsive to change as patients progress from MCI to dementia. The lumbar puncture is performed at entry and after completion of the study protocol. The APoE testing will only be performed at baseline.

Baseline and completion (3-month) cognitive testing will include the Quick Dementia Rating System (QDRS), estimated clinical dementia rating (CDR) scale level, Mini-Mental Status Evaluation (MMSE), Montreal Cognitive Examination (MoCA), and Alzheimer's Disease Assessment Scale (ADAS-Cog12). Upon completion of the protocol intervention, participants will also be asked to report a Global Rating of Change (GRC) score in addition to the neuropsychological testing battery.

All participants will be administered the NE3107 and instructed to maintain a consistent daily dosage of 20 mg BID for the three-month active intervention period. Primary endpoints will involve a comparison of neurophysiological health as evaluated by multi-modal brain MRIs and neuropsychological testing obtained at baseline and post-intervention termination (3 months) (See *2.1: Primary Outcomes* and *2.2: Secondary Outcomes* for detailed descriptions of the MRI modalities and neuropsychological tests, respectively). Additional procedures include blood and serum samples to be collected at baseline and completion to ensure participant safety and effect of NE3107 on laboratory values (See *6.6.1 Laboratory Parameters*).

6.1 Informed Consent

Prior to administration of NE3107, informed consent must be obtained by the participant. The principal investigator, all sub-investigators, and the research coordinator may obtain consent from the subject. All consenting will be done behind closed doors in the privacy of a medical exam room. The participant will be allowed to take home the consent form if he/she needs more time to review the document. The participant will be read the consent form out loud by the member of the study staff obtaining consent. As part of the study criteria, the participant will be required to be cognitively aware and understand the English language. Therefore, the participant's consent should be viewed as their own, and without any undue influence or coercion. If the participant feels uncomfortable, he/she may have an impartial witness of their choice enter the room for the consenting process.

Before signing the consent form, the member of the study staff obtaining consent will verbally ask the participant if he/she has any questions regarding the consent form. If the participant says no, the member of the study staff will ask if all information in the consent form was understood. If the participant says yes, then a member of the study staff will ask if the participant consents to being in this study. If the participant says yes, he/she is ready to sign the consent form.

The principal investigator, all sub-investigators, and the research coordinator may obtain consent from the participant. Once the participant has agreed to be in the study and has signed the consent form, the documentation will exist both physically and electronically. The consent form will be scanned into a computer in which it will be stored under the appropriate folders designated for this research study. The computer will be locked under username, password, and firewall, and will only be accessible by the study staff. The physical version of the consent form will be stored behind lock and key in a drawer or cabinet designated for this research study. The key will also only be accessible by the study staff.

6.2 Medical History

Participants for the present study will be primarily recruited through the primary investigator's medical practice. As patients, participants will have completed intake forms including medical history and any relevant neurological evaluations previously completed. All participants will be required to report on all previous medications for 30 days prior to the study, as well as for the duration of the study. Memantine and acetylcholine esterase inhibitors, donepezil and rivastigmine, are permitted as co-medications in the proposed study. Per the Investigator's Brochure, no drug-drug PK interactions with co-medications memantine, donepezil, galantamine and rivastigmine are expected with the proposed dose of 20 mg BID. As noted in the exclusion criteria, patients with contraindications for lumbar puncture (such as bleeding abnormalities requiring the use of anticoagulant medications) will not be permitted into the study. Additionally, participants with any active cancer requiring chemotherapy will not be permitted to take part in the study.

6.3 Physical Examination

The Principal Investigator (PI) and study doctor will be responsible for performing physical examinations of the participants prior to study participation. As routine practice in the clinic, patients will have filled out a complete demographic questionnaire, undergone a physical examination at first visit, and have had their vital signs recorded. The nervous system is the primary body system to be included in the examination and routine demographics including height and weight will be noted.

6.4 Vital Signs

The PI will be responsible for performing the physical examination of the participant. During in-person study visits, resting heart rate, blood pressure, and temperature will be measured. Blood pressure and heart rate will be monitored using the same machine and same arm upon each visit. The physical exam will not include a pelvic, rectal, or breast exam. Additionally, participants will answer a health and medication questionnaire, disclosing relevant medical history and past or present medications.

6.5 Electrocardiography and Continuous Telemetry Monitoring

6.5.1 12-Lead Electrocardiograms

ECG monitoring is not required during this study but may be requested by the study doctor.

6.5.2 Continuous Holter Monitoring

A continuous Holter monitor is not required during this study but may be requested by the study doctor.

6.6 Clinical Laboratory Tests

6.6.1 Laboratory Parameters

Participants will be in a seated or supine position during blood collection. Clinical laboratory tests (to be collected at baseline, 2 weeks, 4 weeks, 8 weeks, and completion) include the following:

Collected at Baseline and Completion:

Hematology:

- Complete Blood Count with Differential
- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Hemoglobin A1c
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Inflammatory Markers:

- Appearance
- Chlamydia pneumoniae serology (IgG/IgM)
- TNF (tumor necrosis factor)
- Cytokine Panel 13
- hsCRP (highly sensitive c-reactive protein)
- ESR (erythrocyte sedimentation rate)
- HSV (herpes simplex virus serology, IgG/IgM)
- CMV (cytomegalovirus serology, IgG/IgM)
- Helicobacter pylori - breath test
- Lymphocyte Subset Panel 4: CD4 & CD8
- Vasoactive intestinal peptide

Serum Chemistry:

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Amylase
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- Creatine kinase and subtypes
- Gamma-glutamyl transferase (GGT)
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Lipase
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total protein
- Triglycerides
- Troponins
- Uric acid
- Zinc
- Ethanolamine phospholipids

- TGF -b1
- Alpha Melanocyte stimulating hormone
- Beta Melanocyte Stimulating Hormone
- C4A
- ACTH, Plasma (Adrenocorticotropic hormone)
- Anti-gliadin antibodies
- VEGF
- Gastrointestinal tract acids (GTAs)
- MMP-9
- Quantitative immunoglobulins
- Lyme Antibody
- Bartonella quintana antibodies

Urinalysis, complete

- Glucose
- pH
- Bilirubin
- Ketones
- Nitrite
- Uric acid
- WBC, RBC, epithelial cell count

Collected at Weeks 2, 4, and 8:

- Amylase
- Lipase
- Potassium
- Calcium
- Complete Blood Count (CBC) with Differential
- Ethanolamine plasmalogens
- DHA ethanolamine phospholipids
- Choline phospholipids
- Choline plasmalogens
- DHA choline phospholipids
- Dietary fatty acids (omega-3, omega-6, omega-9, OA, LA, AA)
- Iron
- Methyltransferase/choline system
- Phosphatidylethanolamines
- Phosphatidylcholine
- Sphingomyelins
- Ceramides
- Homocysteine
- Elongase 5 activity
- Peroxisomal function
- DHA, EPA
- Triacylglycerols
- Cholesterol total (Fasting)
- HDL (Fasting)
- LDL (Fasting)
-

- Hemoglobin A1c
- Glucose
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Creatine Phosphokinase
- Cholesterol total (Fasting)
- HDL (Fasting)
- LDL (Fasting)
- Triglycerides (Fasting)

Collected Prior to Lumbar Puncture Procedure:

- Prothrombin time
- International Normalized Ratio
- Partial thromboplastin time
- Platelet count

6.6.2 Sample Collection, Storage, and Shipping

After screening, laboratory orders will be written by the study physician which can be taken to any Quest Diagnostics, LabCorp, or any other clinical laboratory. Additional serum will be drawn at the primary study site and sent for analysis to Prodrome Sciences (40880 County Center Drive, Suite R, Temecula, CA 92591, USA). Samples will be shipped on ice and labeled adhering to federal biological substance shipping regulations.

6.7 Dispensing Study Drug

The Manufacturer will supply sufficient quantities of the study formulation for the following: (1) completion of this study and (2) retention, as per applicable regulations. All drug supplies provided for this study will be stored in a secure area with restricted access, under controlled storage conditions described in the product package labelling, unless otherwise instructed per protocol.

Records will be made of receipt and dispensing of NE3107 supplied. It is the responsibility of the Manufacturer to ensure that all drug supplies provided for the study are manufactured under current Good Manufacturing Practices (cGMP) and are suitable for human use.

6.8 Pharmacokinetic Assessments

NE3107 is an orally bioavailable, blood-brain barrier permeable, uncharged, low molecular weight molecule (MW 330.46, LogD = 2), poly-hydroxylated synthetic derivative of the C-19 adrenal steroid series. *In vitro* studies have been conducted to measure membrane transport, active efflux/P-gp interaction, hepatic stability, CYP inhibition, and CYP induction. Numerous pharmacokinetics (PK) studies of NE3107 have been performed in various animal species using single and multiple doses exploring different routes of administration. Oral NE3107 PK studies have been performed in mice, rats, rabbits, dogs, and monkeys. PK following parenteral administration in support of absolute oral availability measurements has also been studied in mice and monkeys. Numerous non-GLP PK studies have been conducted in mice to support formulation development, but only a few that are most relevant to the clinical drug product are summarized below. GLP PK studies have been conducted in rats (Sprague Dawley) and dogs (beagles) concurrent with toxicology studies. No stand-alone single dose GLP PK studies were conducted. All GLP PK studies in rats and dogs have been conducted as part of multiple dose toxicology studies. PK studies have been conducted in rat toxicology studies with oral gavage of NE3107 formulated as an aqueous solution in 30% sulfobutyl ether-cyclodextrin (formulation code HERF202) and as an aqueous suspension of micronized NE3107 (vehicle contained 1 mg/mL sodium carboxymethyl cellulose [CMC], 9 mg/mL sodium chloride, and 20 mg/mL polysorbate-80, 0.5 mg/mL phenol (formulation code HERF405). PK studies have been conducted in dogs with soluble NE3107 (HERF202) and with micronized NE3107 formulated in hard gelatin capsules containing sodium lauryl sulfate, polyplasdone XL 10, microcrystalline cellulose, and magnesium stearate in proportions similar to the NE3107 clinical capsule formulation used for all human studies. NE3107 exists as a single polymorph in all lots of drug substance. All PK studies of crystalline NE3107 used the same polymorph, which is the same polymorph used in human studies.

6.9 Adverse Events Assessments

Following all of the inclusion/exclusion criteria may help to reduce the occurrence of severe adverse reactions. Both the principal investigator and sub-investigators are medical doctors, and are licensed in the state of California, and are in close communication the primary IND holder (BioVie, Inc.) regarding safety monitoring. We will be performing routine patient calls and standard monitoring of side effects due to these medications, as discussed elsewhere in this report. Following these guidelines, side effects can be identified early enough to mitigate any significant or permanent side effects.

6.9.1 Timing

NE3107 has no specific dose-limiting toxicity to guide stopping criteria for laboratory values for safety monitoring. Abnormal lab values will be reviewed in the context of patient safety and potential relationship with NE3107 treatment and NE3107 prior safety data. The investigator may terminate a patient's participation in the trial due to abnormal lab values irrespective the lab values potential relationship with NE3107 treatment.

6.9.2 Severity

The term "severe" describes the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as severe headache). This means it is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

The severity of all AEs will be graded by the PI/Sub-Investigator or a medical qualified delegate according to the following
definitions:

Mild: Adverse event resulting in discomfort, but not sufficient to cause interference in normal daily activities.

Moderate: Adverse event resulting in discomfort that is sufficient to cause interference in daily activities.

Severe: Adverse event resulting in discomfort causing an inability to carry out daily activities.

6.9.3 Relationship

The PI/Sub-Investigator will assess the relationship of all adverse reactions to NE3107 using the following scale:

Probable: A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and which other drugs, chemicals or underlying disease provide plausible explanation.

Unrelated: This category is applicable to AEs which are judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.) and do not meet the criteria for drug relationship listed for the above-mentioned conditions.

All AEs will be evaluated by the PI/Sub-Investigator, who must approve the subject for subsequent dosing.

Any AEs, whether serious or non-serious, will be monitored throughout the study and followed to resolution, when possible, regardless of whether the subject is still participating in the study.

6.9.4 Expectedness

The principal investigator and study doctor will be responsible for determining whether an SAE is expected or unexpected as per drug labels. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

6.9.5 Clinical Significance

Clinical laboratory data collected during the course of the study, which exceeds or drops below the acceptable limits for the participant population and which, based on baseline values, are considered by the Investigator to be clinically significant, will be reported as an AE. If clinically significant abnormal laboratory values lead to, or are associated with clinical symptom(s), they will be reported as an AE.

6.9.6 Serious Adverse Events

6.9.6.1 Definition

A serious adverse event (SAE) is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.9.6.2 Reporting Serious Adverse Events

All serious adverse events (SAEs), whether or not the event is deemed study drug- related, will be reported to the Sponsor by telephone within 24 hours of becoming aware of SAE, followed by a written report within five business days.

Reports of all SAEs will be communicated as soon as possible to the appropriate Institutional Review Board (IRB) and/or reported in accordance with local laws and regulations.

6.10 Concomitant Medication Assessments

Participant medications will be assessed by PI and study staff upon initial screening for the study. Participants will be admitted as a patient under the PI and will fill out a comprehensive demographics form (including past and present medications), which will be subsequently stored in the patient's chart. Concomitant medications will be stabilized for 30 days prior to enrollment in the study protocol.

6.11 Removal of Participants from the Trial or Study Drug

The investigator may withdraw a subject from trial participation for any of the following reasons:

- A protocol violation occurs,
- A serious or intolerable adverse event occurs,
- A clinically significant change in a laboratory parameter occurs,
- The sponsor or investigator terminates the study, or
- The subject requests to be discontinued from the study.

7 STUDY ACTIVITIES

7.1 Screening Visit & Baseline Measure Collection (Days –10 to -1)

Study Screening may take place during an initial visit with study staff to obtain the following assessments, which will be recorded in participant's source documentation/medical record and on the Case Report Form (CRF):

- Participant ID number generation
- Demographic information
- Medical history
- Vital signs
- Height, weight, and calculation of BMI
- Prior/concomitant medications (must be stabilized for 30 days prior to study entry)
- Quick Dementia Rating Scale (QDRS)
- Clinical Dementia Rating (CDR) score, derived from QDRS
- Confirming eligibility (no exclusionary criteria are met)

Baseline measure acquisition may take place over the subsequent 9 days prior to starting the active study intervention, which will include the following:

- Lumbar puncture to test for AB42 and Tau protein levels
- APoE genotyping
- Advanced brain MRI
    - T1, T2, SWI, Neuromelanin, BOLD, ASL perfusion, DTI-NODDI, MRS of the precuneus
- Cognitive examination including:
    - Montreal Cognitive Assessment (MoCA)
    - Mini-mental Status Examination (MMSE)
    - Alzheimer's Disease Assessment Scale (ADAS-Cog12)
- Blood tests for:
    - Complete blood count + diff
    - Creatinine clearance
    - Thyroid hormone panel
    - Electrolytes
    - Inflammatory markers (hsCRP, TNFα, CD4, CD8, absolute neutrophils)

- Quantitative immunoglobulins
- Total and direct bilirubin
- Hemoglobin

- ProdromeScan blood test for:
  - Phosphatidylethanolamines
  - Choline
  - Mitochondrial function

7.2 Clinic Admission (Day 0)

On Day 0, each study participant will be provided with enough NE3107 capsules to maintain a 20mg bid dosage for the three-month active intervention period. Participants will be instructed to take each dosage spaced approximately 12 hours apart.

7.3 Treatment Period (Day 1 to Day 90)

The drug under investigation is NE3107 (17a-ethynyl-androst-5-ene-3b,7b,17b-triol). NE3107 is formulated with common excipients used in oral medications in #2 hard gelatin capsules. The capsules are designed for oral administration. NE3107 capsules are stable at room temperature for at least 18 months. Stability of the capsules used in this study will be monitored by a concurrent stability study conducted by the capsule manufacturer and the holder of the primary IND, Biovie, Inc (Santa Monica, CA).

The rationale for 3-month administration is to allow sufficient time for detectable change to occur. To minimize risk, participants will be called within 24 hours following initiation of the drug and weekly thereafter, as well as meet with the study doctor 1 week after starting the NE3107 regimen and attending once-monthly visits thereafter with the principal investigator to evaluate for safety and tolerability of the study intervention for the duration of the study protocol. These visits will include evaluations of the following:

- Vital signs
- Height, weight, and calculation of BMI
- Documenting changes in concomitant medications
- Participant reports of tolerability
- Evaluation for AEs
- Assessing compliance with the study drug

Additionally, specific laboratory tests will be repeated at weeks 2, 4, and 8 to ensure safety (***6.6.1 Laboratory Parameters).*** Mild, moderate, and severe adverse reactions will be reported on an ongoing basis. Previously observed adverse reactions are listed

in Table 22 of the Investigator's Brochure. Participants will be discontinued if they have moderate or severe adverse reaction ratings according to the **ICH SAE E2A**.

7.4 Early Termination Procedures

Early termination assessments will include the full battery of neuropsychological testing, advanced MRI, and lumbar puncture to the extent that a participant is willing to undergo these follow-up assessments. The minimum assessment required for early termination is a clinical evaluation by the study physician to assess for patient safety and provide instructions to return the study drug.

7.5 Follow-up Visit (Day 90 ± 15)

At the 3-month follow-up visit, the following assessments will be performed and recorded in the participant's source documentation/medical record and on the CRF:

- Vital signs
- Weight
- Concomitant medications
- AEs
- Quick Dementia Rating Scale (QDRS)
- Clinical Dementia Rating (CDR) score, derived from QDRS
- Lumbar puncture to test for AB42 and Tau protein levels
- Advanced brain MRI
    - T1, T2, SWI, Neuromelanin, BOLD, ASL perfusion, DTI-NODDI, MRS of the precuneus
- Cognitive examination including:
    - Montreal Cognitive Assessment (MoCA)
    - Mini-mental Status Examination (MMSE)
    - Alzheimer's Disease Assessment Scale (ADAS-Cog12)
- Blood tests for:
    - Complete blood count + diff
    - Creatinine clearance
    - Thyroid hormone panel
    - Electrolytes
    - Inflammatory markers (hsCRP, TNFα, CD4, CD8, absolute neutrophils)

- Quantitative immunoglobulins
- Total and direct bilirubin
- Hemoglobin

- ProdromeScan blood test for:
  - Phosphatidylethanolamines
  - Choline
  - Mitochondrial function

Note: NE3107 was not teratogenic in rat and rabbit safety studies. Sexually active male and female patients on study should continue using barrier method contraception for 72 hours (three days) after the last dose of NE3107 (terminal plasma t1/2 6-8 hours). The outcome of any pregnancy conceived by a patient on study will be followed to term and the results (normal or detailed description of abnormalities) will be collected as part of the study data and reported to the primary IND holder (Biovie, Inc,).

8 QUALITY CONTROL AND ASSURANCE

BioVie Inc. is encouraged to visit The Regenesis Project at their convenience. The Principal Investigator (PI) and study staff will provide upon request source documents and/or other study-related documents. The PI will maintain regular written and telephone communication with BioVie Inc. In addition, to ensure quality data and standardization, The Regenesis Project will send monthly status reports to BioVie Inc.

All data will be recorded in accordance with good clinical practice (GCP) to ensure accuracy, completeness, legibility, and timeliness of the data reported. All data will be recorded directly on the source documents and will be considered source data. This data will be transferred to Case Report Forms (CRFs). Source data and CRFs will be kept on site at The Regenesis Project. All records and documents pertaining to the study will be retained by The Regenesis Project for at least five (5) years from the completion of the study and will be available for inspection by the Sponsor and Regulatory Agencies.

All source documents and laboratory reports will be Quality Control reviewed to ensure accuracy and completeness. Adverse events will be reviewed and assessed for severity according to the ICH SAE E2A, dated 27 October 1994, by the PI. Specific processes of the study, source documentation and case report forms, and any reports will be audited internally within The Regenesis Project and may be subject to audit by BioVie Inc.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Statistical analyses will be performed by the statistician on staff with The Regenesis Project. Software for statistical analyses will include Microsoft Excel (version 14 or newer) and IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). Statistical analyses will be run to compare change from baseline at the post-intervention termination follow-up (three months after baseline) using a level of significance of 0.05.

A single unblinded interim analysis may be performed when 30% to 50% of the participants have completed the final follow-up timepoint. The purposes of this interim analysis are to declare futility, study discontinuation for overwhelming efficacy, or sample size re-estimation. The sample size will not be reduced based on interim data.

The primary analysis model for the efficacy endpoints will be an MMRM analysis. All available data will be included in these models with no imputation for missing data. Supportive analyses of efficacy data may be conducted to evaluate different methods of handling missing data (i.e., Last Observation Carried Forward, Baseline Observation Carried Forward, multiple imputation for missing data, etc.). These supportive analyses will be detailed in the SAP. Each endpoint within the neuropsychological testing family will be analyzed using MMRM analysis methods in a similar manner as to how the primary endpoints will be analyzed. Formal significance for a given hypothesis will only be declared if that hypothesis is significant and all hypotheses within the family preceding it are significant. This approach will ensure strong type 1 error control is present for all statistical tests conducted.

9.2 Determination of Sample Size

Approximately 25 participants are expected to be enrolled in this Phase II trial to evaluate longitudinal findings from multimodal MRI among the population that is being studied. The study population is sufficiently broad and the conditions of interest are sufficiently prevalent so that recruitment of participants is not a limiting factor for the trial site.

The sample size was chosen according to a power analysis calculated with 80% power and a significance level of 0.05. To achieve completion data for at least 20 participants, enrollment of 25 participants will allow for 20% attrition while maintaining statistical integrity.

9.3 Analysis Populations

Approximately 25 older adults (aged 50-89 years) are expected to be enrolled in this Phase II trial to evaluate longitudinal findings from multimodal MRI.

Populations to be analyzed in the study include the Full Analysis Population (all participants who received any study drug and who participated in at least one post-baseline assessment), Per Protocol Population (all participants who adhere to the major

criteria in the protocol and who did not substantially deviate from the protocol), Safety Population (all participants who received any study drug, excluding participants who drop out prior to receiving any study drug). Evaluable participants (those with baseline and completed follow-up data) will be included in final statistical analyses.

Data may be excluded from analysis on the basis of participant non-compliance with the protocol. Outliers will be identified by testing including Pierce's Criterion, Chauvenet's Criterion, Grubb's test for outliers, and Dixon Q's test. If necessary to address outliers, the statistician will employ standard Winsorization techniques.

The primary analysis model for the efficacy endpoints will be an MMRM analysis. All available data will be included in these models with no imputation for missing data. Supportive analyses of efficacy data may be conducted to evaluate different methods of handling missing data (i.e., Last Observation Carried Forward, Baseline Observation Carried Forward, multiple imputation for missing data, etc.).

9.4 Demographics and Baseline Characteristics

Demographic data to be collected will include age, gender, and number of years from onset of memory complaints in addition to CDR level (as derived from QDRS score) gathered at baseline and final follow-up (three months post-baseline). Results may be stratified by CDR at baseline to see if there is a correlation between baseline CDR and strength of clinical response.

9.5 Statistical Analysis of Endpoints

Based on published annual progression rates ranging from 15-35%, the investigative team determined that this study subset could yield a proportional expected progression rate of 4-9% among study participants over the 3-month study duration. (Maioli et al., 2007; McKann et al., 2011; Amieva et al., 2009; Mitchell & Shiri-Feshki, 2009; Schmidtke & Hermeneit, 2008; Albert et al., 2011; Mashour et al., 2019). Statistical analysis for primary and secondary endpoints will utilize standard evaluations for categorical data.

Primary endpoints will involve a comparison of neurophysiological health as evaluated by multi-modal brain MRIs obtained at baseline and post-intervention termination (3 months). Specifically, multi-modal MRI endpoints will include: An increase or stabilization in glutathione levels (as measured by magnetic resonance spectroscopy, MRS) compared to baseline. Patients with cognitive decline often show characteristic change in MRS or volumetric evaluation compared to age-matched controls (Kuhn et al. 2021); Stabilized and/or improved dendritic density compared to baseline (as measured by diffusion tensor imaging, DTI-NODDI); Enhancement of arterial signal compared to baseline (as quantified by arterial spin labeling, ASL). Patients with cognitive decline often have decreased perfusion in temporal parietal or frontal regions of the brain with ASL perfusion (Kuhn et al. 2021); Increased functional connectivity of the nucleus basalis of Meynert (NBM) with both hippocampi as well as between both hippocampi compared to baseline, as visualized by seed analysis of blood-oxygen level dependent (BOLD) imaging as well as increased neurovascular coupling compared to baseline.

9.5.1 *Statistical Analysis for Primary Imaging Endpoints*

Repeated Measures ANOVAs (RMANOVAs) will be employed to evaluate whether the participants who successfully complete the treatment protocol demonstrate differential improvement in cognition over time with global and domain level mean T-scores as the outcome variable of interest. The same ANOVA-based statistical analysis paradigms will be applied to the neuroimaging data after it is preprocessed. RMANOVAs will be run to determine whether the treatment group demonstrated improvements in the below imaging modalities, from baseline to study completion. Age, sex, and education, as statistically indicated, will be included as additional regressors. Correlation analyses will then be conducted to determine whether absolute change in domain level as measured by neuropsychological evaluation and global cognitive performance is associated with absolute change in the following imaging parameters. To compare individuals from the study population with a "normal" population, Z-score will be calculated for each individual for each component of the toolbox as well as compute a global-cognitive Z-score metric. This will allow the comparison of individual participants to a large population of normal derived from the published literature (e.g. Human Connectome Project).

Global volumetric loss and regional atrophy is a common radiological finding related to AD progression. A disproportionate loss is expected in the temporal-parietal regions and hippocampal structures compared to age-matched controls in the study population (Rabinovici et al., 2007; Whitwell et al., 2011). T1 images will be corrected for field biasing. Then, using FMRIB's Automated Segmentation Tool (FAST), T1 images will be skull-stripped and linearly registered to standard MNI space. Each patient's T1 image will be segmented into 100 cortical and 15 subcortical areas using the Harvard-Oxford Cortical and Subcortical structural atlas in conjunction with fslmaths. Mean volume will be computed for each of these regions for each patient with fslstats (Smith 2002; Manera 2020). The investigative team will use Freesurfer version 6.0 (longitudinal recon-all function) to obtain volumetric measures of 68 segmented cortical volumes and 70 cortical thicknesses. Global volumetric loss and regional atrophy is a common radiological finding related to AD progression. Regional volumes will be analyzed (statistically corrected for intracranial volume) from baseline – 3 months compared to age-matched controls; significant volumetric change is not expected to be seen over the course of treatment with NE3107. Nevertheless, additional analyses will be conducted to determine if demographic or treatment variables predict change in regional volume. Correlation will assess the relationship between neuromelanin change and functional outcomes.

Magnetic resonance spectroscopy (MRS) can detect biochemical changes in the brain related to loss of neuronal interactivity and other neurodegenerative pathology underlying dementia of the Alzheimer's type (Graff-Radford & Kantaci, 2013). MRS data will be processed using Osirix (https://www.osirix-viewer.com/osirix/osirix-md/) and Tarquin (http://tarquin.sourceforge.net/) to calculate neurotransmitter specific peak heights from which neurotransmitter comparison ratios (e.g. NAA/Gl) can be computed. MRS values will be creatine adjusted to improve the likelihood that data was derived from tissue and not CSF. Literature consistently reports on a ratio of decline between the NAA and Creatine (Cr) peaks

among patients with AD (Modrego & Fayed, 2011). A Wilcoxon Signed-rank test will be performed in R (https://www.rstudio.com/) to statistically analyze the changes in the NAA:Cr ratio from baseline to completion of NE3107 protocol. In addition, glutathione levels decrease with redox stress, and declines in glutathione levels have been reported on among patients with AD (Mandal, Saharan, Tripathi & Murari, 2015b). It is anticipated that participants will demonstrate improvement (elevation) of glutathione levels compared to baseline as a signal of overall improvement in bioenergetics. Glutathione levels after NE3107 intervention will be compared to baseline levels with a Wilcoxon Signed rank test in R. Correlation will assess the relationship between neuromelanin change and functional outcomes.

Noradrenergic dysfunction has been associated with the cognitive decline seen in Alzheimer's disease (Peterson & Li, 2018). Pathological alteration to the locus coeruleus, a major source of noradrenaline in the brain, has been implicated in neurodegenerative processes (Betts, Kirilina, Otaduy, Ivanov, Acosta-Cabronero, Callaghan, et al., 2019). Locus coeruleus integrity can be assessed by looking at signal intensity on a Neuromelanin-sensitive MRI. Decreased signal intensity in the locus coeruleus is expected as dementia progresses (Olivieri, Lagarde, Lehericy, Valabrègue, Michel, Macé et al., 2019). Longitudinal changes in locus coeruleus signal will be evaluated visually by a blinded neurologist. Participant change will be analyzed relative to expected rates of dropout/loss. Correlation will assess the relationship between neuromelanin change and functional outcomes.

By measuring free-water changes and the integrity of white matter tracts, DTI can indirectly measure changes caused by amyloid plaque deposition (Wen, Risacher, Xie, Li, Harezlak, Farlow et al., 2021; Alexander, Lee, Lazar & Field, 2007; Smith, Johansen-Berg, Jenkinson, Rueckert, Nichols, Miller et al., 2007). The post-NE3107 DTI metric [fractional anisotropy (FA) and mean, axial and radial diffusivity (MD, AD, RD)] image will be subtracted from the baseline image to produce change images (Fu, Shrestha, Sun, Wu, Luo, Zhang, et al., 2019). Neurite orientation dispersion and density imaging (NODDI) uses a three-compartment model to probe brain tissue microstructure: (1) Free Water Fraction (FWF) which estimates the extent of CSF contamination, (2) Neurite Density index (NDI) which quantifies the packing density of axons/dendrites, and (3) Orientation Dispersion index (ODI) which assesses the coherence of neurites (Fu et al., 2019; Zarei, Patenaude, Damoiseaux, Morgese, Smith, Matthews et al., 2010).

Limited literature using NODDI has been produced in-vivo in mild-cognitive impairment subjects, but the current results show it to be more sensitive/robust than traditional FA values (Fu et al., 2019). Similar to ASL, the three indexes will be compared between baseline/follow-up values. It would be expected that an increase in NDI and a decrease in ODI/FWF to correspond with an improvement in brain health (Fu et al., 2019). Here, an established tract-based spatial statistics (tbss) approach will be used to assess the relationship between voxel-wise changes in white matter integrity (Fu et al., 2019). Additionally, graph theory will be applied to quantify the effect of NE3107 on hippocampal connectivity and associate this effect with cross-sectional and longitudinal cognitive performance (Wen et al., 2021). Lastly, probabilistic tractography will be used to simulate white matter connectivity

between the hippocampus formations (Zarei et al., 2010) and Nucleus Basalis of Meynert. The baseline and follow-up will similarly be compared. Again, RMANOVA will compare pre-and post-NE3107 treatment and within group analyses will assess network predictors of response to NE3107 treatment. All imaging analyses will be corrected for multiple comparisons, both across voxel and between analyses.

Arterial Spin Labeling (ASL) data will be processed and analyzed using FSLs Bayesian Inference for ASL MRI (BASIL; Chappell, Groves, Whitcher & Woolrich, 2009; Woolrich, Chiarelli, Gallichan, Perthen & Lie, 2006). ASL scans yield a perfusion image with voxel values representing local perfusion rates; perfusion difference will be calculated (subtracting tagged/control pairs) and averaged to create a mean perfusion-weighted image (Chen, Wolk & Reddin, 2011). Quantification to cerebral blood flow (CBF) values (milliliters of blood per 100 g of tissue per minute) will be implemented using an estimate of the equilibrium magnetization of arterial blood and the mean perfusion values (Ahlgren, Wirestam, Knutsson & Petersen, 2018; Hernandez-Garcia & Jahanian, 2010). Given the variability of ASL across patients, CBF data will be examined as a ratio to mean grey matter signal.

Each participant's ASL data will be linearly to each his or her T1-weighted image; images will then be transferred to MNI space using non-linear registration in FSL. Within FSL, a voxel-wise between groups (normal vs MRI) comparison of perfusion, corrected for multiple comparisons, will be performed. A repeated measures comparison within subject for pre-vs post intervention ASL as well as between groups will be used to compare effects of NE3107 to normals. Demographic covariates will be included in the model as indicated. All imaging analyses will be corrected for multiple comparisons, both across voxel and between analyses.

Existing literature consistently demonstrates a dropout of signal seen in the temporal parietal lobes among individuals with dementia of the probable Alzheimer's type (Zhang, Gordon & Goldberg, 2017). The mean perfusion values per voxel in the temporal parietal regions will be measured and used to generate a statistical output of participant values relative to a normative, age-matched database. This will test the hypothesis that there will be either stabilization or improvement of voxel signal among participant scans compared with the normative database associated with NE3107.

Reported trends in BOLD imaging follow dementia progression from earlier stages of decline (e.g., CDR = 0.5, characterized by initial hippocampal hyper connectivity) to progressive stages of dementia (CDR $\geq$ 1) and ultimate loss of hippocampal connectivity (Wang, Zang, He, Liang, Zhang, Tian et al., 2006; Sperling, 2011). Processing of resting state (rs) fMRI will include correcting for motion artifacts (using framewise displacement calculations, and within-subject independent component analysis), scrubbing, unwarping and spatial smoothing (FWHM = 5mm). rsFMRI data will be linearly registered to stereotaxic MNI space and co-registered with anatomic, T1 data for each participant.

Two approaches will be used to test rs-network differences. First, the hub of the default mode network atlas will be used as a seed region for each subject, and multivariate exploratory linear optimized decomposition into independence components (MELODIC) will be used to

identify the brain regions whose time series correlate significantly with the hub (Erhardt, Rachakonda, Bedrick, Allen, Adali & Calhoun, 2011). Between-groups comparison of these correlation maps will identify differences in default and salience network integrity. A matrix for each subject will then be made from correlations of time series between each node.

Subsequently, ANOVA will be used to assess group comparisons of the connection strength between nodes, within networks and between networks. All of these analyses will be conducted both within diagnostic group (e.g. within healthy control group only) and between diagnostic groups (i.e. compare effects in cognitive impairment and control groups). Finally, time series correlations will be assessed between multiple regions of interest implicated in the literature in Alzheimer's disease (hippocampal formation, Nucleus Basalis of Meynert (NBM), and other seeds) and the rest of the brain to generate functional connectivity maps (Salami, Pudas & Nyberg, 2014; Li, Jia, Qi, Fan, Ma, Ni et al., 2017; Miao, Wu, Li, Chen & Yao, 2011). Then, between-group comparison will identify differences in the connectivity/network integrity of these regions. Finally, within-group regressions will be used to determine which neural network factors predict response to NE3107 treatment. Age, sex, education, and neuropsychological assessment, as needed, will be included as additional regressors. All imaging analyses will be corrected for multiple comparisons, both across voxel and between analyses.

For the seed-based analysis, after spatial normalization of the images, a standard ROI of the bilateral hippocampi will be drawn on the images using a priori anatomic segmentation. A seed reference time course will be obtained by averaging the survived time courses within the ROI. Correlation analyses will be carried out between the seed reference and the whole brain in a voxel-wise manner. The percent signal change will be extracted from within the same ROI across multiple scan acquisitions and compare an individual's change relative to expected levels of change. Existing literature suggests that a relatively higher activation of hippocampal activity precedes a steeper slope of cognitive decline. Individuals with a baseline CDR of 0.5 will typically demonstrate a decrease in fMRI activity in the hippocampus, and individuals with more rapid decline in their neuropsychological testing scores will have higher hippocampal activation at baseline, and the greatest loss of hippocampal activation over time (O'Brien, O'Keefe, LaViolette, DeLuca, Blacker, Dickerson, & Sperling, 2010). We will compare between baseline, pre-NE3107 and post-NE3107.

Further, BOLD-activity changes will be assessed within a standard ROI (e.g., hippocampus; conventionally defined using a priori anatomic segmentation). To do so, the percent signal change within the same ROI across multiple scan acquisitions will be extracted to compare an individual participant's change relative to expected levels of change. The degree of this change will be correlated with NE3107 treatment and other neural network and behavioral changes to further elucidate the intricacies of the NE3107 treatment. A decrease in neurovascular coupling is expected (as shown and evaluated voxel-wise) globally and regionally in the locus coeruleus and temporal parietal lobes compared to age-matched controls. With NE3107 intervention, it is hypothesized that participants will yield improvement in neurovascular response from baseline. This will be analyzed relative to the normative database and expected decline.

9.5.2 *Statistical Considerations for Secondary Endpoints*

Secondary endpoints will include a longitudinal comparison of metabolic and serological analysis (specifically measures of glucose and insulin homeostasis); the level of cognitive impairment as defined by neuropsychological testing (QDRS/CDR, MMSE, ADAS-Cog, and MoCA scores). Thresholds for reporting clinically meaningful change will include references to published minimal clinically important differences (MCIDs) for each measure. Paired samples t-tests will be used to statistically analyze each secondary endpoint, including the cognitive measures described below as well as changes in serological markers.

The ADAS-Cog evaluates participants' cognitive abilities. It is composed of 11 parts that measure word recall, object/figure naming, command following, constructional praxis, ideational praxis, orientation, word recognition, test direction recall, spoken language, comprehension, and word-finding difficulty. The ASAS-COG is scored from 0-70 by measuring the errors made in each task, with a score of 70 representing the most severe impairment. A point reduction of 3.1 to 3.8 has been found to be the minimal clinically important difference (Schrag & Schott, 2012).

The MMSE is a 30-point questionnaire that evaluates cognition. The MMSE includes specific tasks that assess orientation, attention, memory, language and visual-spatial skills. MMSE scores range from 0 – 30 possible points; 0-17: severe cognitive impairment, 18-23: mild cognitive impairment, 24-30: no cognitive impairment. A point decrease >/= to 3 on the MMSE has been identified as the minimally clinically important difference (Andres, 2019).

The MoCA evaluates frontal-executive functions (e.g., verbal abstraction and mental calculation), language (e.g., confrontation naming, phonemic fluency), orientation (e.g., person, place, date, day of the week, and time), visuospatial construction (e.g., simple figure copy), divided visual attention, and immediate and delayed memory of unstructured information (Nasreddine, Phillips, Bédoran, Charbonneau, Whitehead, Collin, et al., 2005). MoCA scores range from 0-30 possible points; 26 or greater is considered to reflect normal cognitive status.

The Quick Dementia Rating Scale (QDRS) is an interview-based tool administered by study officials to participants' caregivers used to obtain observations from a consistent source (Berman, Koscik, Clark, Mueller, Bluder, Galvin et al., 2017) . The QDRS form consists of 10 categorical questions (5 cognitive, 5 functional), each with 5 detailed options depicting the level of impairment as either 0 (normal), 0.5 (mild/inconsistent impairment), 1 (mild/consistent impairment), 2 (moderate impairment), or 3 (severe impairment). Based on the conversion table outlined in Dr. James Galvin's research (2015), total QDRS scores were converted to Clinical Dementia Rating (CDR) scale levels ranging from 0 (normal aging), 0.5 (mild cognitive impairment), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).

9.6 Safety Analysis

Mild, moderate and severe adverse effects/reactions and mortality will be monitored to confirm the safety and tolerability of NE3107 in the study population. Blood tests and

clinical monitoring will be performed according to standard practice for these agents. Participants will be discontinued if they have moderate or severe adverse reaction ratings according to the ICH SAE E2A. Unexpected or excess serious adverse reaction and excess mortality will result in early termination of the study. Suspected unexpected serious adverse reactions, life threatening reactions and mortality will be reported to the FDA by way of the primary IND holder (Biovie, Inc.) as required under 21 CFR 312.32(c)(1)(v). These reports will be recorded in a lab notebook that will be locked away in a cabinet requiring a key that only the study staff will have access to. This information will also be transcribed to a computer file that will be kept behind username and password.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Principal Investigator: Sheldon E. Jordan, MD

Sheldon Jordan MD, Inc. dba The Regenesis Project
2811 Wilshire Blvd., Suites #690 & 790, Santa Monica, CA 90403
Phone number: (310) 829-5968

10.2 Institutional Review Board (IRB) Approval

Prior to study initiation, institutional review board (IRB) approval shall be obtained and proof shall be provided to all regulatory agencies. The IRB submission for NE3107-TRP-001 "A Phase II Open Label Study for the Use of Anti-Inflammatory, Insulin Sensitizing NE3107 for the Treatment of Cognitive Decline Due to Degenerative Dementias" is awaiting final review and approval from Advarra IRB (Pr#00058626). All reviews and approval by the IRB will be in accordance with Good Clinical Practice (GCP).

In the event of any serious adverse events, the IRB will be notified by the study sponsor.

10.3 Ethical Conduct of the Study

All aspects of this trial shall be conducted in compliance with all applicable federal, state, and local laws and regulations. In particular, the study protocol will be conducted in accordance with generally accepted standards of good clinical practice, informed consent for human participants, and conflict of interest policies related to conduct in clinical research. The Principal Investigator will be responsible for the conduct of the study and oversight of the clinical research staff, all of whom will remain in full compliance with the protocol.

10.4 Participant Information and Consent

The clinical research staff shall obtain from each participant, prior to screening or official entry in the study protocol, a signed informed consent and necessary authorization to disclose health information to BioVie in a form approved in writing by the IRB. The principal investigator, all sub-investigators, and the research coordinator may obtain consent from the participant. In obtaining and documenting informed consent, the investigator will comply with the applicable regulatory requirements and will adhere to good clinical practice and the ethical principles that have their origin in the Declaration of Helsinki. The written informed consent form and any other written information provided to participants will be revised whenever new information becomes available that may be relevant to the participant's consent. Any revised written informed consent form and written information will receive IRB approval in advance of use. Neither the investigator, nor the study staff, will coerce or unduly influence a patient to participate or continue participation in a trial. All consenting will be done behind closed doors in the privacy of a medical exam room. The participant will be allowed to take home the consent form if he/she needs more time to review the document. The participant will be read the consent form out loud by the member of the study staff

obtaining consent. As part of the study criteria, the participant will be required to be cognitively aware and understand the English language. Therefore, the participant's consent should be viewed as their own, and without any undue influence or coercion. If the participant feels uncomfortable, he/she may have an impartial witness of their choice enter the room for the consenting process.

Before signing the consent form, the member of the study staff obtaining consent will verbally ask the participant if he/she has any questions regarding the consent form. If the participant says no, the member of the study staff will ask if all information in the consent form was understood. If the participant says yes, then a member of the study staff will ask if the participant consents to being in this study. If the participant says yes, he/she is ready to sign the consent form.

As stated in the Process of Consent section, all consent by the participant will be done behind closed doors in a private medical exam office. Once the participant has agreed to be in the study and has signed the consent form, the documentation will exist both physically and electronically. The consent form will be scanned into a computer in which it will be stored under the appropriate folders designated for this research study. The computer will be locked under username, password, and firewall, and will only be accessible by the study staff. The physical version of the consent form will be stored behind lock and key in a drawer or cabinet designated for this research study. The key will also only be accessible by the study staff.

10.5 Participant Confidentiality

All participant data will be protected and kept private during the study in compliance with federal, state, and local regulations. All documentation collected by the study staff and Sponsor will be kept confidential. The name and identity of the participants will remain confidential. Any physical data, such as a lab notebook used to record data during the study, will be kept under lock and key. Any digital data will be kept under username and password. Both physical and digital data will only be accessible by the research staff.

The study staff and sponsor shall comply with applicable laws and regulations, as amended from time to time, including without limitation, the Health Insurance Portability and Accountability Act of 1996 and its implementing regulations (HIPAA) with respect to the collection, use, storage, and disclosure of Protected Health Information (PHI) as defined in HIPAA. All study-related PHI shall be collected, stored, used, accessed, and disclosed only as permitted by the IRB-approved informed consent form or HIPAA authorization form obtained from a study participant. BioVie's ability to review participants' study-related information contained in the study participants' medical records shall be subject to reasonable safeguards for the protection of study participant confidentiality and the study participants' informed consent forms or HIPAA authorization forms. BioVie shall not attempt to identify, or contact, any Study participant unless permitted by the informed consent form or HIPAA authorization form.

10.6 Study Monitoring

The primary investigator, Dr. Sheldon E. Jordan, is responsible for monitoring the study site and study activities. Dr. Jordan is on staff at Providence Saint John's Medical Center which is within one to two miles of the clinical site of Sheldon Jordan MD, Inc. dba The Regenesis Project at 2811 Wilshire Blvd, Santa Monica, 90403. The clinical site has five on-campus physicians with Advanced Cardiovascular Support certification and a crash cart, resuscitation equipment and a nursing staff including an RN which are all on site.

All participant data will be recorded on-site at The Regenesis Project. All participant data will be kept private, and all post-processing will be done internally.

The Principal Investigator will assign internal audits to be performed at least twice per month for the duration of the study protocol.

10.7 Case Report Forms and Study Records

Source documents used for this study include neurocognitive examination packets, lab results, raw and post-processed neuroimaging data, and screening forms. Data from source documents will be transferred to case report forms (CRFs) using anonymized participation identification numbers. CRF forms are created and modified by The Regenesis Project staff. The Principal Investigator and clinical research staff will provide BioVie with any and all CRFs and safety-monitoring reports related to the study; all of which will be submitted to the IRB as required. During the study and for at least two years following the completion of the study at all sites, the study staff and Principal Investigator shall promptly provide BioVie with the written report of any findings, including study results and any routine monitoring findings, monitoring reports, and data safety monitoring committee reports including, but not limited to, data and safety analyses, and any study information that may (a) affect the safety and welfare of current or former study participants, or (b) influence the conduct of the study.

10.8 Protocol Violations/Deviations

Deviations from the protocol which will be considered protocol violations include late "out-of-window" follow-up telephone and in-person visits and missed testing appointments. These deviations will be reported in the final clinical study report.

10.9 Access to Source Documentation

Study participants will be able to access copies of source documents upon request following completion of the study protocol.

The study site acknowledges that trial-related monitoring audits, regulatory inspection(s), and regular IRB review are expected, and will make direct access to source data and documents available for review by the proper regulatory agencies.

10.10 Data Generation and Analysis

All study data will be processed on site at Sheldon Jordan MD, Inc. dba The Regenesis Project. All participant data will be protected and kept private during the study in compliance with federal, state, and local regulations. Any physical data, such as a lab notebook used to record data during the study, will be kept under lock and key. Any digital data will be kept under username and password. Both physical and digital data will only be accessible by the research staff.

The clinical database will be generated using Microsoft Excel (version 14 or newer) and analyzed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

Data will be entered by authorized clinical research staff on a weekly basis. Database entries will be checked for accuracy and completion at the time of internal audits, to be performed at a minimum of twice per month throughout the study.

10.11 Retention of Data

The study staff shall retain and preserve a copy of the study records for the longer of (a) five (5) years following the termination of the study protocol.

10.12 Financial Disclosure

The investigative team and the Sponsor understand that the amount of any payment made on behalf of research conduct may be disclosed and made public by either party as required by law or regulation, including the Patient Protection and Affordable Care Act of 2010, provided that the disclosure clearly designates the payment as having been made to the Sponsor Institution (The Regenesis Project) and not to the Principal Investigator or physician.

10.13 Publication and Disclosure Policy

The investigative team shall have the right to publish, present, or use any study data for its teaching, research, education, clinical and commercial purposes without the payment of royalties or other fees. However, the investigative team, including the Principal Investigator, will not use or provide any drug performance data to any third party for commercial benefit. With respect to publications of any study data, the contents (including scientific conclusions and professional judgments) of any paper submitted shall be determined by the Principal Investigator in the exercise of reasonable judgment. The Principal Investigator shall provide the Sponsor with a copy of papers prepared for publication at the earliest practicable time, but in any event not less than sixty (60) days prior to the submission to a scientific journal or presentation at scientific meetings and a reasonably detailed summary or abstract of any other oral or written publication not less than sixty (60) days prior to their submission or presentation. The investigative team shall consider any and all comments made by BioVie in good faith; BioVie personnel shall be acknowledged in accordance with customary scientific practice; authorship shall be determined in accordance with the standards of the International

Committee of Medical Journal Editors (ICMJE). If during BioVie's review, BioVie finds that any publication contains BioVie Confidential Information, BioVie shall have thirty (30) days from the date of receipt from the investigative team to respond with a request to remove such Confidential Information. The Principal Investigator agrees that any publication or other public disclosure shall include an acknowledgement of BioVie's support of the study, and if applicable, support of the development of the publication or disclosure. BioVie shall be entitled to make and use copies of the publication made by the Principal Investigator in relation to the study. The sixty (60) day minimum lead time for publication or disclosure may be shortened by mutual consent by both Parties in writing.

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Appendix 1 Schedule of Events

Evaluation	Screening Days -10 to -1	Clinic Visit Day 0	Treatment Period Day 1 - 90								Follow-up (Days 91 ± 15)
			Day 1	Day 7	Day 15	Day 30	Day 45	Day 60	Day 75	Day 90	
Informed Consent	X										
I/E Criteria	X	X									
Demographics	X										
Medical History	X										
Physical Examination	X	X		X		X		X		X	X
Advanced MRI of the Brain	X										X
Lumbar Puncture	X										X
Cognitive Testing	X									X	X
APoE Genotyping	X										
Vital Signs	X	X		X		X		X		X	X
Laboratory Tests	X				X	X		X		X	X
Participant ID Assignment	X										
AE Assessment			X	X	X	X	X	X	X	X	X
Conmed Assessment	X	X	X	X	X	X	X	X	X	X	X
Discharge From Clinic											X

Appendix 2 Sponsor Signatures

Study Title:	A Phase II, Open-Label Study for the Use of Anti-Inflammatory, Insulin-Sensitizing NE3107 for Treatment of Cognitive Decline Due to Degenerative Dementia
Study Number:	NE3107-TRP-001
Final Date:	Final V1.0 (4 November 2021)
Amendment 1 Date:	

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed:_____ Date:_____

Sheldon E. Jordan, MD Inc.
Principal Investigator
Sheldon Jordan MD Inc., dba The Regenesis Project
2811 Wilshire Blvd., Suite #790, Santa Monica, CA 90403
(310) 829-5968

Appendix 3 Investigator's Signature

Study Title:	A Phase II, Open-Label Study for the Use of Anti-Inflammatory, Insulin-Sensitizing NE3107 for Treatment of Cognitive Decline Due to Degenerative Dementia
Study Number:	NE3107-TRP-001
Final Date:	Final V1.0 (4 November 2021)
Amendment 1 Date:	{revision date}

The information contained in this protocol and all other information relevant to NE3107 are the confidential and proprietary information of Sheldon E. Jordan, MD Inc., dba The Regenesis Project, and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Sheldon Jordan MD Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I agree to comply with all applicable regulations and to conduct the study as described herein, in accordance with applicable national, state, and local regulations, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Sheldon Jordan MD, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about NE3107 and the study.

Signed:_____ Date:_____

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