Washington University in St. Louis

Clinical Study Protocol:

DIAN-TU-001

A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive, and Clinical Endpoints in Dominantly Inherited Alzheimer's Disease

Regulatory Sponsor:	**Washington University in St. Louis** **Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU)** **Department of Neurology, Campus Box 8111** **660 S. Euclid** **Saint Louis, MO 63110**
Study Drugs:	**Gantenerumab (RO4909832), E2814, and Lecanemab (BAN2401)**
Protocol Number:	**DIAN-TU-001**
Investigational Phase:	**II/III**
Protocol Version:	**Amendment 13**
Version Date:	**05 Apr 2023**
IND Number:	**115,652**
EudraCT Number:	**2013-000307-17**

INVESTIGATOR'S STATEMENT

I understand that all information concerning the product(s) supplied to me by Washington University in St. Louis, in connection with this study and not previously published, is confidential information. This information includes the Investigator's Brochure, protocol (and applicable amendments), Case Report Forms, assay methods, technical methodology, and basic scientific data.

I will conduct the study according to the protocol and I understand that any changes to the protocol must be approved in writing by Washington University in St. Louis, and the Institutional Review Board/Independent Ethics Committee (IRB/IEC) before implementation, except where necessary to eliminate apparent immediate hazards to the participants.

I confirm that I will report all adverse events and product complaints following the regulations referenced in the protocol.

I confirm that I will conduct this study in conformance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) as described in the United States (US) Code of Federal Regulations, 21 CFR Parts 11, 50, 54, and 312 (as applicable) and the ICH E6 guideline, and U.S. law and regulations or in conformance with the principles of the Declaration of Helsinki, GCP, and local laws and regulations if my site is located outside the US.

I confirm that I am informed of the need for records retention and that no data will be destroyed without the written consent of Washington University in St. Louis.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol dated 05 Apr 2023.

Investigator's Signature: _____ _____

Date

Name (printed): _____

MASTER PROTOCOL PLATFORM SYNOPSIS

Protocol Number	DIAN-TU-001
Protocol Title	A Phase II/III multicenter, randomized, double-blind, placebo-controlled platform trial of potential disease modifying therapies utilizing biomarker, cognitive, and clinical endpoints in dominantly inherited Alzheimer's disease
Clinical Phase	Phase II/III
Investigators	Investigators will be selected based on patient population and clinical research competency.
Study Centers	Approximately 40 sites globally. The currently existing Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) sites will continue to be active for new study drug enrollment and new sites will continue to be identified and qualified.
Study Objective	To assess the safety, tolerability, biomarker, cognitive and clinical efficacy of investigational products in participants with an Alzheimer's disease-causing mutation by determining if treatment with the study drug slows the rate of progression of cognitive/clinical impairment or improves disease-related biomarkers.
Study Population	Participants who are either known to have a mutation causing Alzheimer's disease OR who do not know their gene status but are "at-risk" for a dominantly inherited Alzheimer's disease (DIAD) mutation AND who are either 1) cognitively normal and are between 10 years younger (−10) to 10 years older (+10) than their expected age at symptom onset or 2) have mild symptoms of dementia (Clinical Dementia Rating [CDR] 0.5 or 1). Individual drug arms may require genetic disclosure to participate based on their specific design. For the cognitive run-in (CRI) period only, the study population will be expanded to include participants who have a DIAD mutation in the family AND are cognitively normal and who are 11 to 25 years younger (−25 to −11) than their estimated age of symptom onset in order to include participants for future trials that may have differences in the enrollment age of onset.
Study Design	This is an adaptive platform-based study, which allows flexibility to add a new compound to the same protocol, allowing participants to be randomized to study drug arms open to enrollment, and to maintain a cohort of trial ready participants with or at risk for DIAD mutations. The study has three periods: a CRI period, a double-blind treatment period, and an open-label extension period, which may differ by drug arm. Data may be pooled from the placebo groups of different drug arms, from the CRI period, and from the DIAN Observational (DIAN-OBS) study to serve as pooled controls for treatment efficacy evaluation per the inclusion and exclusion of each drug arm.

	Previously, DIAN-TU-001 also included a double-blind gantenerumab, solanezumab, and atabecestat arm. For further information relevant to these arms, see earlier versions of the protocol. Participants enrolled to double-blind drug arms are treated with active drug or placebo, while biomarker (e.g., positron emission tomography (PET) imaging, volumetric brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), and plasma measures), clinical, cognitive, and safety assessments are monitored throughout the study period. Starting with Amendment 8 of this protocol, a CRI period was opened for recruitment if no relevant study drug arms are randomizing to drug or placebo. The biomarker, cognitive and clinical endpoints may be used to conduct interim analyses in any of the study drug arms; a study drug arm may be stopped early or revised (e.g., dose adjustment or treatment duration) based upon the results of the interim analyses or information from other clinical trials for the same drug, as outlined in each drug-specific appendix. The study has a common close design included in specified drug arms, in which double-blind treatment is continued for all participants until the last participant enrolled completes the 4-year randomized period of treatment or withdraws. Mutation positive participants will be randomized to active drug or placebo at a ratio specified in each drug-specific appendix. Groups enrolled simultaneously will be balanced by a minimization algorithm including clinical state and stage of disease measures (CDR-SB, years from onset) and other factors (gene type [*APP, PSEN1, PSEN2*] years of education, age, presence of an *APOE ε4* allele, region, study site and gender). When not excluded in an individual drug arm, participants who are mutation negative will be assigned placebo. At the request of participants, mutation negative participants may be included to maintain blinding as to genetic status for those who do not wish to know their genetic status. Mutation negative participants may be included in individual drug arms when feasible and appropriate. Participants who are mutation negative will be assigned placebo. Data from mutation negative participants will be used to develop models for longitudinal changes in biomarkers and cognition in healthy adult controls.
Number of Participants	This study will recruit participants from the Dominantly Inherited Alzheimer Network observational study (DIAN-OBS), a multicenter international study supported by the National Institutes of Health (Grant Number U01-AG032438; RJ Bateman), Dominantly Inherited Alzheimer Network Trial Units (DIAN-TU) sites, DIAN-TU partner sites, DIAN Expanded Registry (DIAN-EXR), and families identified by the sites.

	The number of participants for each drug arm is specified in each drug-specific appendix. Recruitment is limited to those with a baseline CDR 0 to 1 (inclusive). There may be up to 740 participants recruited into the CRI period while new drugs are implemented. Up to 500 Secondary Prevention CRI participants may be enrolled for (estimated years from symptom onset (EYO) −10 to +10) drug arms, in order to ensure that a sufficient number of active and eligible participants qualify for entry into a study drug arm during randomization. In addition, up to 240 Primary Prevention (EYO −25 to −11 and cognitively normal [Clinical Dementia Rating (CDR) 0]) participants may be enrolled in the CRI period to establish a randomization-ready cohort of participants.
Main Inclusion Criteria	Participants must meet ALL inclusion criteria. The main inclusion criteria are as follows: • –10 to +10 EYO (secondary prevention population): within −10 to +10 years (inclusive) of the estimated age at symptom onset, CDR 0 to 1, inclusive, known eligible mutation carrier or at 50% risk (affected parent or sibling) • −25 to −11 EYO (primary prevention population): within 11 to 25 years younger than their estimated age at symptom onset, CDR 0, known carrier or mutation in their family pedigree; if the at-risk parent is deemed a non-carrier at any point, participant will be withdrawn from study • Willing to complete the main study-related testing, evaluations, and procedures
Main Exclusion Criteria	Participants will be excluded if they have a major or unstable illness that would prevent trial participation or are unable to complete main study-related testing. Exclusions include MRI contraindications, required anticoagulation therapy, and pregnancy. Participants who know they are mutation non-carriers are not eligible.
Route and Dosage Form	Route and dosage forms are included in each drug-specific appendix. There is no study drug administered during the CRI period.
Dosage	Dosage is included in each drug-specific appendix.
Duration of Treatment	The total treatment duration for any blinded study drug arm is determined by the enrollment duration, and is not expected to exceed the sum of the enrollment duration and the planned double-blinded period (e.g. if the enrollment duration is 2 years and treatment is 4 years, the total treatment duration will not exceed 6 years). If the CRI period is open to enrollment, participants may be enrolled in the CRI period. Participants will continue in the CRI period until a study drug arm is opened for randomization, but no longer than approximately 3 years. If a participant is in a CRI period, a minimum of 8 weeks must elapse between the participant's last administration of the cognitive battery during the CRI period

	and administration of the baseline (V2) cognitive battery for a blinded study drug arm. If a study drug arm demonstrates a potential for clinical benefit at the end of the double-blind treatment period, eligible participants may be offered to continue or start treatment, via an open-label extension (OLE) period in which all participants will receive active study drug. The OLE period may last up to an additional 3 years (36 months) or more, or until the treatment becomes commercially available in a participant's country, whichever occurs first.
Primary Outcome Measure	The Primary Outcome is defined in each drug-specific appendix, and may include biomarker, cognitive, or clinical outcomes. Comparisons will be made between each active drug, mutation positive placebos, and control groups, e.g. eligible DIAN-OBS participants. The OLE endpoints are outlined in each drug-specific appendix, if applicable.
Additional Outcome Measures	Additional outcome measures, which may be further categorized as secondary or exploratory in the drug-specific appendices in this or prior amendments, and/or statistical analysis plans (SAPs), include the following: 1. Assess safety and tolerability of each study drug in individuals who have mutations causing dominantly inherited Alzheimer's disease. 2. Biomarker Endpoints used at interim analysis: Assess target engagement with biomarker endpoints specified for each drug based on mechanism of action. Assess AD biomarkers, including soluble biochemical measures (e.g. amyloid-beta and tau), imaging measures of pathology (e.g. amyloid and tau PET), and AD biomarker changes (e.g. atrophy measured by MRI, hypometabolism by FDG PET, and neurodegeneration measured by Neurofilament light). 3. Comparisons between each drug and the placebo arm in change from baseline for the following clinical and cognitive measures listed below: a. Clinical measures to be obtained at baseline, and annual visits will be administered at the host DIAN-TU site include: ▪ Clinical Dementia Rating™ (CDR), including Clinical Dementia Rating Sum of Boxes™ (CDR-SB) ▪ Clinician's diagnostic assessment ▪ Geriatric Depression Scale (GDS) ▪ Neuropsychiatric Inventory Questionnaire (NPI-Q) ▪ Functional Assessment Scale (FAS) ▪ Mini-Mental State Examination (MMSE) – also measured at the 26 week (6 month) time point between annual visits with the below cognitive battery. b. Cognitive measures to be obtained at baseline and every 26 weeks (approx. 6 months) will be administered at the DIAN-TU site or via home health nurse trial-certified cognitive rater include:

	▪ Memory Complaint Questionnaire (MAC-Q) ▪ Buschke and Grober Free and Cued Selective Reminding Test-Immediate Recall (FCSRT-IR) ▪ Wechsler Memory Scale-Revised (WMS-R) Logical Memory/Paragraph Memory (Immediate & Delayed Recall), Alternate Paragraph for Logical Memory I & II - Version A (Immediate and Delayed) and Alternate Paragraph for Logical Memory I & II - Version B (Immediate and Delayed) ▪ Category Fluency (Animals) ▪ Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit-Symbol Substitution Test ▪ Trailmaking Test Parts A & B ▪ Wechsler Memory Scale-Revised (WMS-R) Digit Spatial Span Forward and Backward ▪ Ambulatory Research in Cognition (ARC) smartphone-based cognitive assessments (Grids, Prices, Symbols) 4. Imaging measures obtained in drug arms include the following (see drug-specific appendices and SAPs for outcome classification): a. Glucose metabolism positron emission tomography (PET) imaging with FDG-PET b. Amyloid PET imaging with [^{11}C]PiB-PET c. Tau PET imaging with [^{18}F]MK-6240 d. Structural brain measures with volumetric MRI e. Functional connectivity MRI (fc-MRI) f. Diffusion Tensor Imaging (DTI) MRI, including diffusion basis spectrum imaging (DBSI) g. Blood flow measures by Arterial Spin Labeling (ASL) MRI h. Assessment of MRI features, such as microhemorrhages (MCH), white matter hyperintensities (WMH), cerebral infarctions, and Amyloid Related Imaging Abnormalities (ARIA) on conventional MRI sequences. 5. Fluid biomarker measures that may be included as secondary or exploratory endpoints as specified in the drug-specific appendix and/or SAP, include the following: a. CSF and plasma amyloid species analyses b. CSF and plasma tau species analyses c. CSF and plasma neurofilament light chain analyses d. Additional CSF and blood biomarkers of AD, neurodegeneration, neuroinflammation, or other biomarkers. 6. Assess longitudinal change in biomarker, cognitive, and clinical measures in individuals who do not have mutations causing DIAD (mutation-negative placebo group).

	Additional drug-specific endpoints may be listed in each drug-specific appendix. Refer to the final SAP for drug-specific differentiation of endpoint classification based on the respective drug's target and mechanism of action.
Statistical Considerations	The data collected in the CRI period are able to be used for analysis in the respective drug arm under which participants are randomized and treated and as control data for the DIAN-TU platform. Descriptive statistics: Descriptive statistics will be provided for both safety and efficacy variables at each time point collected by treatment groups and across placebo groups. Continuous variables (e.g., biomarker values) will be summarized using the number of observations, mean, standard deviation, minimum, lower quartile, median, upper quartile, and the maximum. Categorical variables (e.g., presence or absence of an *APOE* ε4 allele) will be summarized using the number and percentage in each category. Safety analyses: Safety analyses will be drug-specific and in general include all participants who consent to participate and are randomized to receive any active study drugs or placebo. Adverse events will be characterized using standard terminology (adverse events, serious adverse events, treatment-emergent serious adverse events). The seriousness and causality of adverse events will be summarized. Interim analyses for biomarker endpoints: Interim biomarker analyses will be conducted for each study drug arm to assess whether the active study drug is engaging its biological target. The timing of the interim analyses may vary for each study drug arm. At each interim, an analysis will be conducted for the biomarker endpoints, comparing the active drug to its own placebo group (direct placebos) or control groups. Pre-specified definitions for early termination for futility will be drug-specific and based on collection of appropriate biomarker assessments following sufficient drug exposure. Details about the interim analyses are described in each drug-specific appendix. Interim analyses for cognitive endpoints: Interim cognitive analyses may be conducted to assess whether active study drug has significant changes in cognitive decline. Details about any planned interim analyses are described in each drug-specific appendix. All interim analyses will be conducted on the modified intent-to-treat (mITT) population, which is defined as all participants who are randomized, treated, and assessed for their primary outcomes at least once after the baseline assessment. Efficacy analyses for the primary endpoint: The primary endpoint efficacy analyses will be conducted on the modified intent-to-treat (mITT) population, unless defined otherwise in the drug-specific appendix or SAP. The primary efficacy hypothesis will be tested by comparing the active drug arm to the control group.

Sample Size Considerations	Drug arm specific sample size considerations are in drug-specific appendices and associated SAPs.

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ABBREVIATIONS/GLOSSARY OF TERMS

Abbreviation/ Term	Definition
[^{11}C]PiB	[^{11}C]-Pittsburgh Compound B (PiB) amyloid PET imaging tracer
[^{18}F]AV-1451	Flortaucipir, a [^{18}F] tau PET imaging tracer, aka T807
[^{18}F]-FDG	Fluorodeoxyglucose PET imaging tracer
[^{18}F]MK-6240	A [^{18}F] tau PET imaging tracer
Aβ	Amyloid beta peptide
$A\beta_{40}$	Amyloid beta peptide fragment with amino acids 1-40
$A\beta_{42}$	Amyloid beta peptide fragment with amino acids 1-42
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADA	Anti-drug antibody; drug-specific testing may include measurement of antibodies directed against the investigational drug
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive Subscale
ADCS	Alzheimer's Disease Cooperative Study
ADCS-ADL	Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (liver function test)
ANCOVA	Analysis of covariance
API	Alzheimer's Prevention Initiative
APOE	Apolipoprotein E genotype, the *APOE ε4* allele is associated with increased risk of developing AD pathology
APP	Amyloid precursor protein
ARC	Ambulatory Research in Cognition is the smartphone-based cognitive testing
ARIA	Amyloid-related imaging abnormalities (includes those that occur both after treatment and during the natural history of untreated Alzheimer's disease)
ARIA-E	Amyloid-related imaging abnormality characterized by vasogenic edema, including both parenchymal and in leptomeningeal spaces

Abbreviation/ Term	Definition
ARIA-H	Amyloid-related imaging abnormality characterized by hemorrhage, including microhemorrhage, macrohemorrhage (e.g., lobar hemorrhage) and superficial hemosiderin deposits
ASL	Arterial spin labeling
AST	Aspartate aminotransferase
$AUC_{0-\tau}$	Area under the concentration – time curve for a drug between time 0 and the end of the dosing interval (τ)
AUC_{Inf}	Area under the concentration – time curve for a drug between time 0 and time infinity
BACE	β-secretase enzyme
BP	Blood pressure
CDR	Clinical Dementia Rating™
CDR-SB	Clinical Dementia Rating Sum of Boxes™
Central laboratory manual	Manual that describes details for processing and shipping of laboratory samples
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments (FDA regulation of clinical laboratories)
C_{max}	Maximum (peak) plasma drug concentration
C_{trough}	Minimum (trough) plasma drug concentration, measured at the end of a dosing interval
Cogstate	A global technology company that supports the use of cognitive measures in clinical trials
Concurrently randomized placebos	The group of mutation-positive participants that were randomized to placebo while another treatment arm was actively randomizing, but were not direct placebos for the other arm(s)
CNS	Central nervous system
CRI	Cognitive run-in
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia suicide severity rating scale

Abbreviation/ Term	Definition
C-SUVR	Composite standardized uptake volume ratio
CV	Curriculum vitae
DAT	Dementia of the Alzheimer's type; symptomatic dementia clinically diagnosed as likely due to Alzheimer's disease pathology
DBSI	Diffusion basis spectrum imaging
DCA	Dominantly Inherited Alzheimer Network Central Archive
DIAD	Dominantly inherited Alzheimer's disease
DIAN-OBS	DIAN Observational study - Dominantly Inherited Alzheimer Network, a multicenter international observational study supported by the National Institutes of Health
DIAN-EXR	Dominantly Inherited Alzheimer Network Expanded Registry; an international repository coordinated by the DIAN-TU whose purpose is to connect researchers with individuals and families affected by the disease
DIAN-MCE	DIAN-Multivariate Cognitive Endpoint
DIAN-NPC	Dominantly Inherited Alzheimer Network-Neuropathology Core
DIAN-TU	Dominantly Inherited Alzheimer Network Trials Unit
DIAN Trials Unit Cognition Core Procedures Manual	Manual providing specific information on procedures for cognitive testing
DIAT	Diaminothiazine
Direct placebos	The group of mutation-positive participants that were randomized to the blinded placebo for a specific treatment
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTI	Diffusion Tensor Imaging
ECG	Electrocardiogram
eCRF	Electronic case report form
EAD	Early Alzheimer's disease
EDC	Electronic data capture

Abbreviation/ Term	Definition
Eligible DIAN-OBS participants	The group of mutation-positive participants that enrolled in the DIAN-OBS study and met the eligibility criteria to be borrowed for the DIAN-TU-001, as defined in the Statistical Analysis Plan (SAP)
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End of study
ET	Early Termination
EYO	Estimated years from symptom onset
FAS	Functional Assessment Scale (previously Functional Assessment Questionnaire [FAQ])
fc-MRI	Functional connectivity MRI
FCSRT-IR	Free and Cued Selective Reminding Test-Immediate Recall
FDA	Food and Drug Administration
FLAIR	Fluid-attention inversion recovery
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
Global Manual of Operations	Manual describing details of DIAN-TU trial operations; see also *the arm-specific DIAN Trials Unit Cognition Core Procedures Manuals,* central laboratory manual, *MRI Technical Manual, PET Technical Procedures Manual* and *Pharmacy Manual.*
GRE	Gradient-recalled echo (MRI sequence)
GUID	Globally Unique Identifier
HCLF	High-concentration liquid formulation
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
Home health nurse	A licensed nurse that is an extension of the trial site and is delegated by a site principal investigator (PI). Home health nurse staffing is provided by a nursing vendor that is contracted through the DIAN-TU. Home health nurses complete visits in participant's home and/or other trial-identified locations. Home health nurses may also complete training to become trial-certified cognitive raters.

Abbreviation/ Term	Definition
Hy's Law case	Situation where there is a 3-fold elevation above upper limit of normal of ALT or AST, accompanied by a two-fold increase of total bilirubin above upper limit of normal, in the absence of other explanations for these changes. This suggests possible drug-induced liver injury.
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IgG1	Monoclonal antibody of the immunoglobulin subclass G1
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system (used only if technological constraints preclude use of interactive web response system)
IWRS	Interactive web response system
LFT	Liver function test
LOCF	Last observation carried forward
LP	Lumbar puncture
Lyo-F	Lyophilized formulation
mAbs	Monoclonal antibodies
MAC-Q	Memory Complaint Questionnaire
MAD	Multiple ascending dose
MAPT	Microtubule-associated protein tau
Mayo-ADIR	Mayo Clinic Aging and Dementia Imaging Research
Mc+ and mc-	Mutation carriers (mc+) and non-carriers or those known not to have an DIAD-causing mutation (mc-)
MCI	Mild cognitive impairment
MCM	Microhemorrhages
MDPM	Multivariate Disease Progression Model

Abbreviation/ Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
Medical Director	The sponsor's Medical Director will lead discussion and make final decisions on reporting of adverse events and other medical issues (e.g., inclusion/exclusion criteria). Some discussions (e.g., regarding ARIA) will include the Project Arm Leaders.
Medical Monitors	The DIAN-TU Medical Director and Project Arm Leaders (PALs) available 24 hours/7 days a week to serve as first contact for sites regarding medical issues.
mITT	Modified intent-to-treat
MMA	Methylmalonic acid
MMRM	Mixed model for repeated measures
MMSE	Mini-Mental State Exam
MRI Technical Manual	Manual providing specific information on procedures for MRI
MRI	Magnetic resonance imaging
MTBR	Microtubule binding region
Mutation positive placebos	Combination of direct placebos and concurrently randomized placebos
NfL	Neurofilament light chain
NFT	Neurofibrillary tangle
NONMEM	A non-linear mixed effects modeling software tool used in population pharmacokinetic-pharmacodynamic analysis
NPC	Neuropathology Core
NPI-Q	Neuropsychiatric Inventory Questionnaire
NYHA	New York Heart Association
OLE	Open-label extension
PD	Pharmacodynamic
PAL	Project Arm Leader. Each study drug arm will have a PAL. This individual will have experience with the same or similar study drugs and will advise the site investigators and Medical Director as needed and will help ensure consistency between sites for each study drug.
Participant	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control.

Abbreviation/ Term	Definition
PET	Positron emission tomography
PET Technical Procedures Manual	Manual providing specific guidance on procedures for PET imaging
PI	Principal investigator; if needed, a site PI may delegate duties to a qualified sub-investigator
Pharmacy Manual	Manual describing specific procedures for pharmacy operations, drug handling and administration
PK	Pharmacokinetic
POCBP	Person of childbearing potential: A post-menarchal, pre-menopausal person who has not had a hysterectomy, bilateral oophorectomy or medically documented ovarian failure. Menopause is defined as amenorrhea for one year in the absence of any other medical or physiological cause for the amenorrhea[1].
Proband	An individual identified by the study team who is known to have a disease-causing mutation; relatives of the proband may be potentially eligible for the study.
PSEN1	Presenilin 1
PSEN2	Presenilin 2
Ptau	Phosphorylated tau protein
$ptau_{181}$	Tau protein phosphorylated at threonine 181
$ptau_{217}$	Tau protein phosphorylated at threonine 217
PT, PTT	Prothrombin time (PT) and partial thromboplastin time (PTT) are measures of blood clotting
Q2W	Every two weeks
Q4W	Every four weeks
QC	Quality control
QT and QTc	Period from the beginning of the QRS complex to the end of the T wave on the ECG
QW	Each week
RBBB	Right bundle branch block

[1] Post-menarchal, pre-menopausal people who have undergone tubal ligation should have pregnancy testing done at all visits as indicated for a person of childbearing potential.

Abbreviation/ Term	Definition
sAD	Sporadic Alzheimer's disease
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
Study partner	A person identified by the participant who agrees to accompany the participant on annual study visits and is able to provide accurate information as to the participant's cognitive and functional abilities to enable completion of scales which require informant, and who signs the necessary consent form if applicable
SUVR	Standardized uptake value ratio (a measurement for PET imaging)
T2*	MRI sequence used to detect hemorrhage
Tau	Tau protein
TEAE	Treatment-emergent adverse event
Tg	Transgenic
TIA	Transient ischemic attack
T_{max}	Time it takes a drug to reach peak plasma concentration after administration
Trial-certified cognitive rater	Any rater that has been certified by the DIAN-TU Cognition Core or designee, as described in the *Cognition Core Procedures Manual*, and may include DIAN-TU staff, trial-certified home health nurses, or study site staff
TSH	Thyroid stimulating hormone
UA	Urinalysis
V	Visit (number)
vMRI	Volumetric magnetic resonance imaging
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WMH	White matter hyperintensities
WMS-R	Wechsler Memory Scale-Revised

1 INTRODUCTION

1.1 Background

This study will recruit participants from the Dominantly Inherited Alzheimer Network (DIAN) observational study, a multicenter international study supported by the National Institutes of Health (Grant Number U01-AG032438; RJ Bateman), Dominantly Inherited Alzheimer Network Trial Units (DIAN-TU) sites, DIAN-TU partner sites, DIAN Expanded Registry (DIAN-EXR), and families identified by the sites. As part of the DIAN-TU-001 protocol, participants undergo longitudinal assessments that include clinical assessment, cognitive testing, magnetic resonance imaging (MRI) and amyloid and tau positron emission tomography (PET) imaging, and analysis of blood and cerebrospinal fluid (CSF).

Participants in DIAN are recruited from families that have at least one member who has been identified as having a mutation linked to dominantly inherited Alzheimer's disease (DIAD). The mutations in presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*) and amyloid precursor protein (*APP*) that are associated with dominantly inherited Alzheimer's disease have very high penetrance (near 100%). This study enrolls individuals who are either known to have a disease-causing mutation or who are at risk for such a mutation (the descendant or sibling of a proband with a known mutation) and unaware of their genetic status. Because the age at onset of cognitive changes is relatively consistent within each family and with each mutation (Ryman, Acosta-Baena et al. 2014), an age at onset is determined for each affected parent or mutation as part of the DIAN Observational study (DIAN-OBS) protocol. This study will enroll participants who are either asymptomatic and are within a specific window of time of expected age at onset for their family and/or mutation or who have symptoms of mild Alzheimer's disease.

The ability to identify individuals destined to develop Alzheimer's disease (AD) and predict the age of onset with a high degree of confidence provides a unique opportunity to assess the efficacy of therapies at asymptomatic and very early stages of dementia. Families with known disease-causing mutations are extremely rare and are geographically dispersed throughout the world. These constraints necessitate a specialized study design. Many of the participants in this study will not yet have any cognitive symptoms of AD; they will be "asymptomatic" carriers of mutations that cause DIAD and would be expected to perform normally on standard cognitive and functional testing. Imaging and fluid biomarkers will be used to demonstrate that the treatment compounds have engaged their therapeutic targets. A set of cognitive measures designed to assess the very earliest and most subtle cognitive changes will be collected. Additionally, because many at-risk individuals decide not to know whether they have the disease-associated mutation or not, when allowable in individual drug arms, some of the at-risk individuals enrolled in this study will not have the disease-causing mutations; they will be "mutation negative". It is important to enroll these participants to avoid coercion (e.g., potential participants may be pressured into genetic testing to learn their genetic status in order to be eligible for the trial) unless the drug-specific design includes open-label treatment. These mutation negative individuals will be assigned to the placebo group and data will be used to

determine normal ranges of outcome measures. Participants and site study staff will remain blinded as to these individuals' active or placebo group assignment and mutation status. Thus, the study will be double-blinded for placebo and for mutation status, except for mutation positive participants who are aware of their genetic status. There may be exceptional circumstances when required by local regulation or health authorities where enrollment may be restricted to mutation carriers only, but such mandates will be thoroughly documented and agreed upon by the governing regulatory agency and sponsor.

This is an adaptive platform-based study (Woodcock, LaVange 2017). Several different therapies (each referred to as a study drug arm) will be tested in order to increase the likelihood that an effective treatment will be discovered. The compounds are selected for this trial based on mechanism of action and available data on efficacy and safety profile. The study design includes a pooled placebo group (referred to as the mutation positive placebos) which may be shared by study drug arms. Mutation positive participants will be assigned to a study drug arm and subsequently randomized within that arm to the active drug to placebo ratio specified in each drug-specific appendix. When included in individual drug arms, mutation negative participants will all receive placebo treatment. Participants and study staff will not be blinded as to which study drug arm each participant has been assigned; they will be blinded as to whether participants have been randomized to active drug or placebo.

Biomarker, cognitive, and/or clinical endpoints will be specified for each study drug arm. Biomarker data will be analyzed for pre-specified endpoints consistent with the drug's mechanism of action and other AD biomarker outcomes.

Interim analyses of the imaging or fluid biomarker endpoint will assess safety and whether each study drug engages its biological targets. The clinical and cognitive assessments are designed to assess subtle cognitive changes that may be detectable before the onset of dementia as well as cognitive and clinical decline in symptomatic groups.

After the last participant in a study drug arm completes the 4-year treatment period, participants in that study drug arm may be eligible to receive active study drug in an open-label extension period (Section 3.9).

Starting with Amendment 8 of this protocol, a cognitive run-in (CRI) period was implemented to allow for enrollment during periods when study drug arms are not randomizing. This enables the DIAN-TU platform to have continuous enrollment during periods before or in-between drug arm randomization.

The CRI period of cognitive, clinical, and imaging data collection was designed as part of the platform study to utilize the time in between enrollment of study drug arms for the purposes outlined in Section 1.4 of this protocol. The CRI period was incorporated into the protocol as specified in the US NIH NexGen grant, which was reviewed and awarded in August 2017 (US NIH Grant R01 AG053267, PI RJ Bateman). Based on the early discontinuation of the atabecestat drug arm in July 2018, the cognitive run-in period was implemented to recruit until the next study drug arm is randomizing to drug and placebo. The CRI period will enhance study

enrollment by identifying eligible participants and engaging them with the cognitive assessments and can reduce practice effects by allowing participants to habituate to the testing process. The CRI further provides important baseline and run-in data that adds control data to the platform and informs about the effects of tested drugs.

In addition, the CRI period was expanded with Amendment 9 of this protocol to allow for inclusion of the DIAD population in the primary prevention stage; further defined in Amendment 11 as the population from 11 to 25 years before estimated symptom onset (−25 to −11, primary prevention population). The CRI period will provide engagement opportunities for the primary prevention population while increasing power and decreasing enrollment timelines for the US NIH trial Grant U01 AG059798 (PI EM McDade), which was reviewed and awarded September 2018.

The data collected in the CRI period will be used for analysis in the respective drug arm under which participants are randomized and treated.

1.2 Drug-specific Background

Complete drug-specific information for each study drug used in this trial is included as a drug-specific appendix to this protocol. Once any specific drug arm is completed, it may be removed in subsequent amendments therefore the applicable details can be found in prior versions of the protocol. Refer to the respective Investigator's Brochures (provided separately) for additional information.

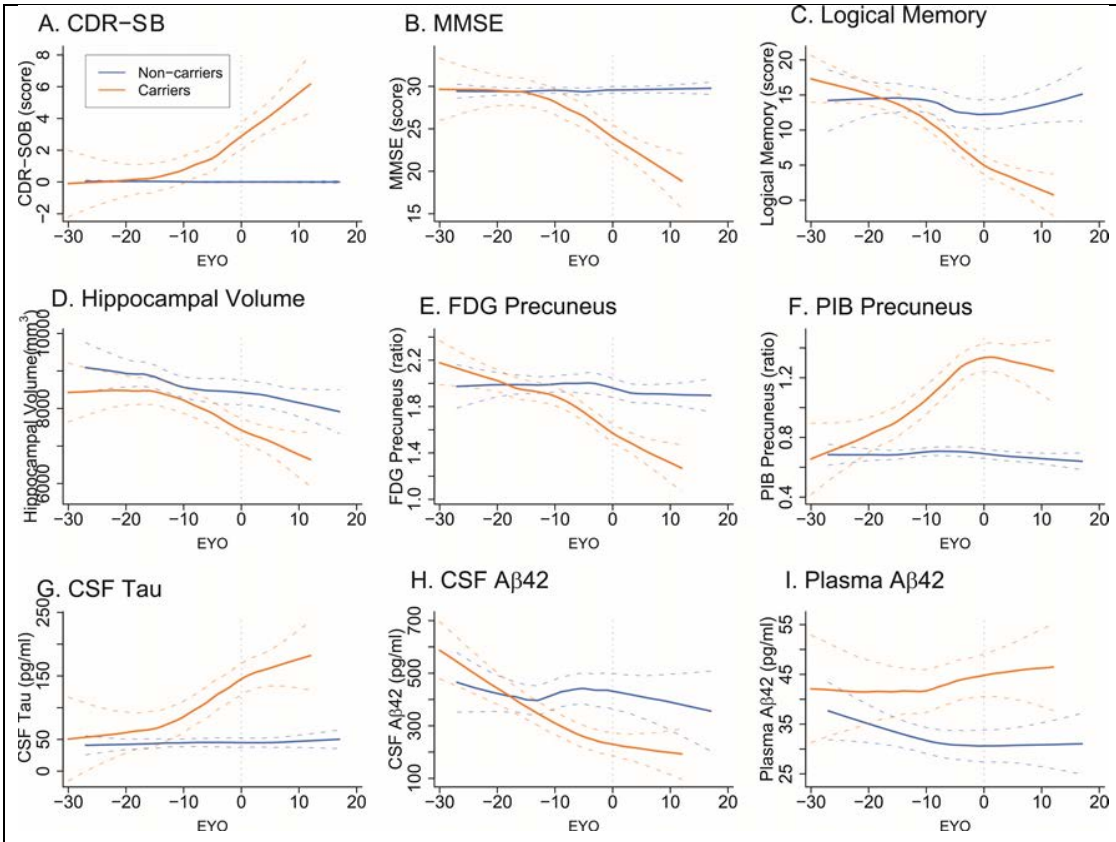
1.3 Rationale for Biomarkers

More than half of the mutation positive participants in this study will have normal cognition per randomization and enrollment criteria and will therefore be "asymptomatic" and without clinical manifestations of dementia of the Alzheimer's type (DAT). The pathological processes that define AD, amyloid plaques and neurofibrillary tangles, start to develop 10 to 20 years before clinical symptoms (Price and Morris 1999; Price, McKeel et al. 2009). Findings from the DIAN observational study (Bateman, Xiong et al. 2012) indicate pathological and biomarker changes occur at least 15 years before the estimated symptom onset in the DIAN cohort. Fluid and imaging biomarkers of amyloid include positron emission tomography (PET) using the amyloid-binding agent [^{11}C]-Pittsburgh Compound B (PiB) ([^{11}C]PiB-PET) (Mintun, Larossa et al. 2006) and cerebrospinal fluid (CSF) levels of amyloid beta peptide 1-42 ($A\beta_{42}$) (Fagan et al, 2006) and the ratio of $A\beta_{42}/A\beta_{40}$ (Lewczuk et al, 2016). CSF total tau (Fagan, Head et al. 2009) and phosphorylated tau181 ($ptau_{181}$), have shown early asymptomatic changes in DIAD (Bateman et al., 2012, et al, 2020) and when combined with $A\beta_{42}$ can predict cognitive decline (Fagan, et al. 2007; Schindler et al., 2017).

Studies in individuals who carry a mutation linked to early onset AD suggest that these biomarker changes are detectable 20 or more years before the anticipated time of disease onset (Figure 1) (Bateman, Xiong et al. 2012; Portelius, Fortea et al. 2012; Ringman, Coppola et al.

2012). Data from the DIAN-OBS study suggests that changes in biomarkers begin with [^{11}C]PiB-PET measures of amyloid burden in the precuneus (Figure 1) followed by changes in CSF total tau, FDG-PET, and cerebral atrophy before clinical decline (Bateman, Xiong et al. 2012).

Figure 1 Cross-sectional Analyses of Clinical, Cognitive, Structural, Metabolic, and Biochemical Changes in Autosomal Dominant Alzheimer's Disease Mutation Carriers versus Non-carriers, According to Estimated Years from Expected Symptom Onset



The clinical and cognitive measures of the CDR-SB (scores range from 0 [cognitive normality] to 18 [maximal cognitive impairment]) (Panel A), the Mini–Mental State Examination (scores range from 0 [severe impairment] to 30 [no impairment]) (Panel B), and the Logical Memory subtest of the Wechsler Memory Scale–Revised (scores range from 0 [no recall] to 25 [complete recall]) (Panel C) showed impaired ratings beginning approximately 5 to 10 years before expected symptom onset (EYO is expected year at onset). MRI measures of hippocampal volume (Panel D) showed increased brain atrophy approximately 15 years before expected symptom onset. Decreases in cerebral glucose metabolism, as measured by positron-emission tomography (PET) with the use of fluorodeoxyglucose (Panel E), occurred approximately 10 years before expected symptom onset, and deposition of amyloid-beta (Aβ) in the precuneus, as measured by PET with the use of Pittsburgh compound B (Panel F), began approximately 15 to 20 years before expected symptom onset. In the cerebrospinal fluid (CSF), levels of tau protein (Panel G) increased beginning 10 to 15 years before expected symptom onset, and levels of $A\beta_{42}$ (Panel H) decreased at least 15 years before expected symptom onset. Plasma $A\beta_{42}$ levels were elevated throughout the range of estimated years from expected symptom onset (Panel I). Dashed lines represent 95% confidence intervals of the fitted curves. SUVR denotes standardized uptake value ratio. Reproduced from Bateman et al., 2012.

Neurofilament light chain (NfL) is an important marker of neurodegeneration in AD. Neurofilament light chain is a neuronal cytoplasmic protein; levels of NfL increase in CSF and blood proportionally to the degree of axonal damage in neurological disorders. Evidence that

both CSF and blood plasma NfL may serve as diagnostic, prognostic and monitoring biomarkers in neurological diseases is progressively increasing, and NfL is one of the most promising biomarkers to be used in clinical and research settings (Gaetani et al. 2019). Neurofilament light chain has previously demonstrated changes in response to therapies in multiple sclerosis and Human Immunodeficiency Virus (HIV) (Varhaug et al. 2019). Although NfL is non-specific for AD, it may allow for a measurement of disease modification in response to the active therapies. Further, NfL has demonstrated pre-symptomatic changes in DIAD 7 to 16 years before symptom onset (Preische et al. 2019).

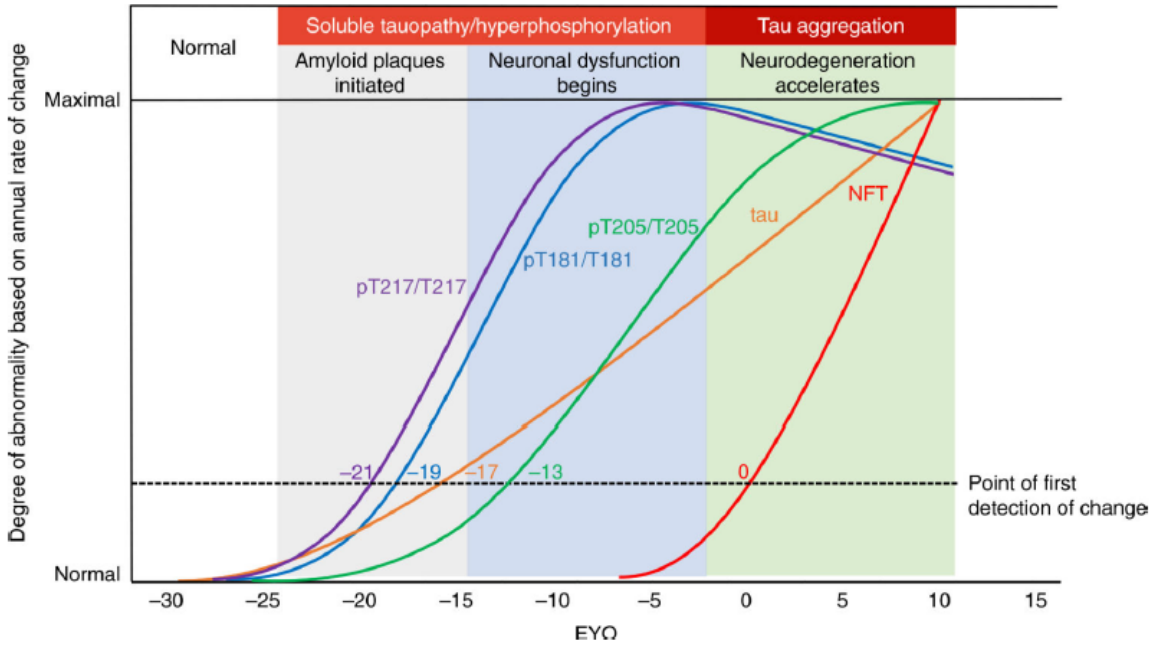
Cortical volume loss (as measured by volumetric MRI [vMRI]) and cerebral metabolism (measured by PET visualization of 2-[^{18}F] fluoro-2-deoxy-D-glucose [FDG-PET]) assess anatomic and metabolic sequelae of neurodegeneration. Substantial literature supports the idea that these biomarkers correlate with pathological disease and may be predictive of clinical outcome. Levels of the CSF biomarkers and [^{11}C]PiB binding correlate with risk of developing dementia in asymptomatic individuals and with the risk of developing more severe impairment in those with very mild dementia or mild cognitive impairment (Hansson, Zetterberg et al. 2006; Fagan, Roe et al. 2007; Li, Sokal et al. 2007; Morris, Roe et al. 2009; Snider, Fagan et al. 2009). In asymptomatic older individuals, increased levels of brain amyloid as detected by increased [^{11}C]PiB-PET signal or reduced CSF Aβ_{42} are not benign as they are associated with increased rates of brain atrophy (Wang, Fagan et al. 2011; Chetelat, Villemagne et al. 2012). Nondemented individuals with amyloid deposition as detected by amyloid PET have poorer performance on episodic memory testing and are more likely to experience cognitive decline (Doraiswamy, Sperling et al. 2012; Sperling, Johnson et al. 2012).

In contrast to Aβ accumulation, autopsy studies suggest that the density and distribution of phosphorylated tau and of neurofibrillary tangles increases during the course of dementia due to AD, with higher levels observed in individuals with mild cognitive impairment and at more severe levels of dementia (Braak and Braak 1995). Tau accumulation may correlate with neurodegeneration across the entire spectrum of the illness (Duyckaerts, Brion et al. 1987; Nelson, Alafuzoff et al. 2012). Aβ accumulation may serve as a biomarker for the earliest stages of disease, while longitudinal and quantitative assessments of the level and extent of tau deposits may better reflect the progression of neurodegeneration over time. Studies of CSF Aβ_{42} and tau levels in participants in the DIAN Observational (DIAN-OBS) study support this idea (Bateman, Xiong et al. 2012; Benzinger, Blazey et al. 2013; Fagan, Xiong et al. 2014). This understanding of sequential changes in tau biomarkers identifying tau stages in DIAD, and a four-fold higher change in tau PET signal in DIAD compared to sporadic AD among symptomatic participants, has greatly improved the potential to detect drug effects in DIAD (Barthélemy et al., 2020, Gordon et al., 2019).

Tau pathology in the brain correlates more closely with clinical status and dementia in AD than amyloid plaques, atrophy, or glucose metabolism (Ossenkoppele et al., 2016). Tau aggregation correlates with onset, progression, and neurologic type and has large significant increases in DIAD relative to healthy normal individuals. Recent evidence demonstrates that tau

pathophysiology evolves through distinct phases in DIAD (Barthélemy et al., 2020), suggesting three sequential phases in biomarker-based models of AD progression as depicted in Figure 2: 1) amyloid accumulation triggers initiation of tau pathophysiology including phosphorylation of soluble tau; 2) soluble tau increases beginning 10-20 years before onset of clinical symptoms based on increases in CSF phosphorylated-tau (soluble tau phase); and 3) tangle spread begins concurrently with clinical symptom onset based on tau PET (tau aggregation phase) (Gordon et al., 2019). The dynamic and diverging patterns of soluble and aggregated tau first begin in close relationship with amyloid pathology with soluble phosphorylation at specific tau sites and sequentially change over the course of the disease (Barthélemy et al., 2020).

Figure 2 Stages of Tau Pathology and Potential Mechanisms to Target Tau



Tau pathophysiology evolves through distinct phases in DIAD. Tau sequentially changes by stage of disease. Starting with the development of fibrillar amyloid pathology, levels of phosphorylation of pT217 (purple) and pT181 (blue) begin to increase. Then, with the increase in neuronal dysfunction (decreased cortical metabolism), levels of pT205 (green) begin to increase, along with soluble t-tau (orange). Lastly, with the onset of neurodegeneration (based on cortical atrophy and clinical decline), tau-PET tangles (red) begin to develop, while pT217 and pT181 phosphorylation ratios decrease.

Source: Barthélemy et al., 2020

The imaging and CSF biomarkers measure different aspects of the AD pathogenic cascade and are correlated with underlying brain pathology. There is some evidence to support the idea that therapeutic interventions can produce detectable changes in these biomarkers in symptomatic individuals with late onset sporadic dementia of the Alzheimer's type (McKhann, Knopman et al. 2011; Mintun, Larossa et al. 2006; Klein et al. 2021).

The DIAN-TU-001 trial provides an opportunity to investigate the potential for tau imaging to enhance basic understanding of the evolution of tau pathology during the AD disease process, to

understand the relationship between tau imaging and tau measurements in CSF and may support a role for tau imaging as a new surrogate biomarker in interventional studies.

The CRI period and future tau NexGen drug arms in the trial platform will use the PET tracer, [^{18}F]MK-6240 (an [^{18}F] tau imaging agent, Cerveau Technologies), that has high affinity for the human phosphorylated tau deposits in AD brain (Hostetler, Walji et al. 2016, Lohith, Bennacef et al. 2016, Walji, Hostetler et al. 2016, Lohith, Bennacef et al. 2017, Neelamegam, Yokell et al. 2017). The inclusion of tau PET imaging will be limited to participants between −10 to +10 years of their estimated years to symptom onset (secondary prevention population) and will provide important data for the longitudinal evolution of tau pathology during the AD disease process, and the relationship of Aβ and tau in disease pathophysiology. Tau imaging during the CRI period will help assess the rate of change in tau pathology in untreated participants, enable appropriate designs of tau-based therapeutics, and provide longitudinal run-in control data to be compared during the randomization period of the study. Tau imaging at the end of the CRI period and during the course of the subsequent treatment period will help assess long-term effects of potentially disease modifying drugs and the rate of change in tau pathology in both treated and untreated (placebo group) participants.

CSF levels of tau and ptau will be used as additional endpoints. These biomarkers may reflect neuronal or axonal injury, as evidenced by the correlation of CSF levels of total tau with the amount of tissue damage and poor clinical outcome in acute brain disorders (Hesse, Rosengren et al. 2000; Ost, Nylen et al. 2006). Levels of ptau measured in CSF samples obtained during life have been shown to correlate with the amount of neocortical tangle pathology at autopsy (Buerger, Ewers et al. 2006; Barthélemy 2020; Mattsson et all, 2020) suggesting it may serve as a marker of tangle pathology. Some studies have shown that elevated tau and ptau alone predict progression from mild cognitive impairment (MCI) to DAT (Blom, Giedraitis et al. 2009), while other studies demonstrate that the ratio of tau(s) to $A\beta_{42}$ are highly predictive of cognitive decline in cognitively normal cohorts (Fagan, Roe et al. 2007; Li, Sokal et al. 2007; Craig-Schapiro, Perrin et al. 2010) as well as individuals with MCI or very mild dementia (Hansson, Zetterberg et al. 2006; Snider, Fagan et al. 2009; Craig-Schapiro, Perrin et al. 2010; Landau, Harvey et al. 2010; Tarawneh, D'Angelo et al. 2011; Buchhave, Minthon et al. 2012). Levels of CSF tau and ptau are also elevated in DIAD mutation carriers during both the presymptomatic and symptomatic stages (Moonis, Swearer et al. 2005; Ringman, Younkin et al. 2008; Bateman, Xiong et al. 2012; Ringman, Coppola et al. 2012).

Antibodies targeting amyloid plaques have impacted the removal of plaques and showed some change in other biomarkers. For example, an OLE of gantenerumab in sporadic AD, with treatment over 36 months after starting up-titration substantially lowered PiB-PET to below the level of amyloid positivity (Klein et al. 2021). A number of other compounds have also shown effects on these biomarkers (Knopman DS, 2021; Mintun MA, 2021; Salloway S, 2021; Swanson CJ, 2021).

These studies support the idea that successful target engagement by the tested compounds would result in a detectable effect on imaging and fluid biomarkers, allowing the use of the

biomarkers as potential predictors of treatment efficacy in individuals at risk for dominantly inherited Alzheimer's disease (Strobel, 2015). The specific biomarker endpoint chosen for each tested study drug will depend on the mechanism of action of the target compound and on available preliminary data on the effects of the therapy on relevant biomarkers (see each drug-specific appendix and respective Investigator's Brochures for additional details).

1.4 Rationale for Cognitive Run-in Assessments

A CRI period may be opened to enrollment prior to randomization into study drug arms added to the platform trial. Run-in periods have several practical advantages, including increasing engagement of participants, establishing rapport with site personnel and personnel for home visits (if applicable), and familiarization of participants with the processes and procedures of the trial (Schechtman et al., 1993; Pablos-Méndez, et al., 1998). One of the most important scientific advantages is a decrease in variability in cognitive test performance. Most participants are unfamiliar with the cognitive testing process and some may be anxious during cognitive testing. Scores from measures acquired during their first exposure to the testing process can therefore be influenced by random and systematic within-person variability. For example, daily variability in sleep quality, fatigue from traveling to a DIAN-TU performance site, or a recent exposure to a stressful event can introduce random variability to assessments. There may also be other factors introduced into cognitive testing that may contribute to variability. Practice effects refer to increases in cognitive scores that appear upon retesting as participants become familiar with the test content, the testing environment, and test concepts and strategies. Typically, these practice effects peak after two to three exposures to test stimuli and diminish with further retesting (Hassenstab et al., 2015; Ivnik et al. 2000). There may be additional variability in test performance due to demand characteristics (the perceived expectation by participants to perform in a certain way to "please" the examiner) or to factors that influence so-called "white-coat" hypertension, where performance may be affected by anxiety about undergoing testing and "exposing" latent cognitive deficits that many participants from DIAD families are highly concerned about. The combined effect of high variability on cognitive performance may impact reliability in cognitive outcomes. A CRI period can reduce the effects of temporal fluctuations in performance by allowing participants to habituate to the testing process, thereby reducing practice effects, demand characteristics and test anxiety. Moreover, results from clinical trials testing the β-secretase enzyme (BACE) inhibitors in those with and at risk for AD have identified evidence of an unanticipated cognitive impairment (Novak, et al., 2020). A CRI period will also offer the opportunity to more easily detect a deleterious drug effect by establishing a reliable baseline in participants where the majority are cognitively normal at trial entry. This is particularly important for those participants that are much younger than their estimated age of onset where a decline in cognition would represent a significant deviation from the expected performance. The CRI period could help identify potential deleterious side effects of therapies at an earlier point and reacting appropriately.

Since the launch of the DIAN-TU-001 study there have been significant advancements in the development of tau PET imaging tracers, including the development of multiple tracers with different properties. Given the recent introduction of [^{18}F]MK-6240 into the DIAN-TU program, there remains some uncertainty relative to the characteristics of earliest detectable levels and the longitudinal change in this tau PET tracer across the different clinical stages of disease. Therefore, the CRI period provides the opportunity to establish a better understanding of the baseline and longitudinal changes of [^{18}F]MK-6240 in the DIAD population and further inform the power estimates for future NexGen study arms in the platform. It also provides improved power to detect drug effect changes on tau PET measures of NFT accumulation.

Recent technological advancements in mass spectrometry have led to increased sensitivity and precision for the longitudinal detection of AD biomarkers in plasma. The pathological cascade of events begins with altered CSF and plasma $A\beta_{42}/A\beta_{40}$ ratio in the preclinical phase of disease. Studies of phosphorylated tau species (e.g., pT217, pT181) in CSF and plasma have demonstrated a strong temporal correlation with Aβ plaque formation, suggesting that certain secondary p-tau measures may also provide information on prevention of Aβ aggregation/accumulation (Barthélemy, et al., 2020). Blood collection in the CRI period provides an opportunity to determine how early in the pathological cascade changes in Aβ, tau, p-tau and MTBR species can be detected and learn more of their predictive capacity of disease onset and/or stage.

1.5 Rationale for Open-label Extension

In dominantly inherited Alzheimer's disease, participants who carry the disease-associated mutation will ultimately develop dementia unless disease modification occurs. This trial is testing the hypothesis that the study drugs can change the course of disease progression and delay or prevent dementia. If the trial demonstrates an intervention has potential clinical benefit and is reasonably safe, an open-label extension for mutation carriers provides the potential for benefit to participants and the opportunity to determine long term effects and assess disease modification. Thus, at the end of the double-blind treatment period, participants may have the opportunity to receive active drug with appropriate safety monitoring; details are provided in Section 3.9.

2 STUDY OBJECTIVE

To assess the safety, tolerability, biomarker, cognitive, and clinical efficacy of investigational products in participants with an Alzheimer's disease-causing mutation by determining if treatment with the study drug improves disease-related biomarkers and slows the rate of progression of cognitive or clinical impairment.

3 STUDY DESIGN

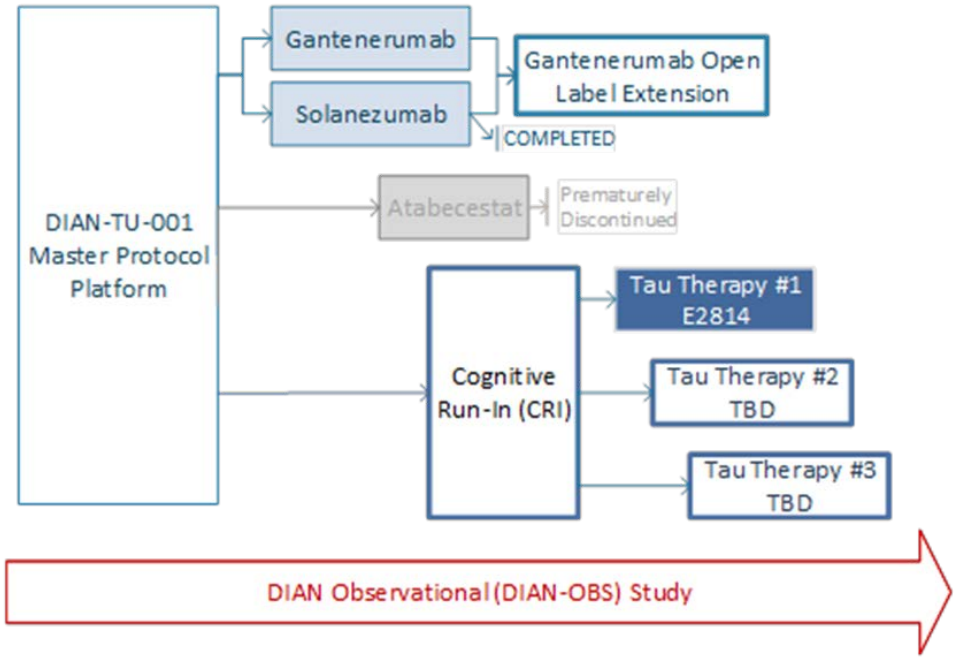
3.1 Overall Design

This is a Phase II/III multicenter randomized, double-blind placebo-controlled, platform trial of potential disease modifying therapies utilizing biomarker, cognitive, and clinical endpoints, in dominantly inherited Alzheimer's disease. Individuals who are at risk for dominantly inherited Alzheimer's disease (known mutation carriers or those who are blind to their mutation status but have a 50% risk of being mutation carriers) AND who are between 10 years younger (−10) up to 10 years older (+10) than the typical age at onset of dementia in their pedigree or gene type (*APP, PSEN1, PSEN2*) AND who are either cognitively normal (Clinical Dementia Rating™ [CDR]=0) or have mild symptoms of dementia (CDR 0.5 or 1) will be enrolled.

In drug arms not requiring genetic disclosure for inclusion, some participants in this study choose to remain blinded to their genetic status (where permitted in the study drug arm(s) design) which may be due to concerns of the impact on their mental well-being, financial, insurance and other life factors. These participants and study staff will remain blinded to their genetic status throughout the study. Mutation negative participants will not receive active study drug, but in order to maintain blinding as to genetic status, mutation negative participants will be assigned to the placebo group and will participate in all study procedures and assessments. Placebo PET tracers may be used if required by local regulations, if pre-approved by the sponsor. Mutation-negative participants will not be included in the primary efficacy or futility analyses. These participants will provide valuable biomarker data that will be useful for future studies in both DIAD and sporadic DAT. Mutation positive participants will be randomized into actively enrolling study drug arms and within a study drug arm the participant will be randomized at a ratio specified in each drug-specific appendix. Therefore, both mutation positive and negative participants will be randomized to receive placebo for each study drug arm. This is needed because the treatment administration routes and safety monitoring may be different for the different study drug arms. Participants and study staff will be blinded as to whether participants are on active drug or placebo but will not be blinded as to the treatment route and interval.

This is an adaptive platform-based study, with flexibility to add new investigational products to the protocol, allowing participants to be randomized to study drug arms open to enrollment, and for the study to maintain a cohort of trial ready participants with or at risk for DIAD mutations. Data from the platform's placebo drug arms will continue to be utilized by subsequent drug arms as control data, in addition to the DIAN-OBS matched control data.

Figure 3 DIAN-TU-001 Master Protocol AD Prevention Platform Design



The first two drug arms tested in the platform were the gantenerumab and solanezumab study drug arms, with each enrolled participant randomized to active drug or the corresponding placebo ("direct placebo"). The double-blind periods concluded for both drug arms with an open-label extension (OLE) of gantenerumab opened to any of the participants enrolled in either of the double-blind drug arms. Changes, such as to the enrollment criteria (e.g., the EYO range for inclusion), may be made based on the specific therapeutic compounds being tested and the stage of disease that is most likely to be targeted by a therapy. Results from the completed solanezumab and gantenerumab arms in DIAN-TU-001, which included an EYO range of −15 to +10, found that close to 30% of participants at an EYO range of −15 to −10 had very low amyloid PET levels, and thus had minimal to no detectable tau pathology. Therefore, the change to the EYO entry criteria for CRI and future tau-based therapeutics to −10 to +10 in Amendment 11 will increase the likelihood of participants having some tau-related changes that can be measured during the double-blind period of the trial. The third drug arm added to the platform was the atabecestat arm which was prematurely discontinued due to safety (Novak, G, et al. 2020). For further information relevant to the completed testing periods of these study drug arms, see earlier version(s) of the protocol.

Additional study drug arms will continue to follow the same core procedures for measuring biomarker, cognitive, and clinical measurements, thereby allowing continued sharing/pooling of placebo data across study drug arms.

Starting with Amendment 8, a CRI period was opened for recruitment and enabled for future drug arms. With Amendment 9, the CRI period was expanded to include 2 participant

populations; the original population of participants within −15 to +10 years of the predicted or actual age at cognitive symptom onset (secondary prevention population) and a younger primary prevention population 18 years of age or older that are younger than −15 years from estimated cognitive symptom onset and CDR 0 (primary prevention population). Amendment 11 refines the primary and secondary prevention populations to −25 to −11, and −10 to +10, respectively. CRI participants must have a minimum of 8 weeks between the participant's last administration of a complete cognitive battery during the CRI period and administration of the baseline (V2) complete cognitive battery. The CRI period will continue until a study drug arm is opened for randomization, but no longer than approximately 3 years. Amendment 13 extends the duration of CRI up to 3 years. Participants having completed 2 years in CRI before Amendment 13 approval may be reconsented once approved for Amendment 13; participants should resume their study visits based on their original CRI Entry date.

The platform is designed to test drugs' engagement of its respective targeted biomarker (phase II period) and those successful in engaging their biomarker target will continue to a clinical and/or cognitive outcome (phase III period). The biomarker endpoints and cognitive endpoints may be used to conduct interim analyses in any of the study drug arms. The design includes the potential to conduct at least one interim analysis of the biomarker and/or cognitive endpoints. The number and timing of interim analyses may vary for each study drug arm. Details about the interim analyses are described in each drug-specific appendix. If a study drug fails to demonstrate target engagement, as evidenced by meeting a pre-specified threshold at one of the interim analyses, the Data Safety Monitoring Board (DSMB) may recommend that a study drug arm either be stopped early or that the study dose be escalated, if dose escalation is deemed safe. If a study drug achieved significant slowing of cognitive decline at the cognitive interim analysis, the study drug arm may be terminated early for efficacy.

Study drug arms that demonstrate a potential clinical benefit may have an open-label extension period.

3.2 Rationale for Study Design

Two unusual features of this study population influenced the study design: 1) maintaining the blind to mutation status, and 2) participant burden. First, many individuals who are at risk for dominantly inherited Alzheimer's disease do not want to know their mutation status. The study design has allowed for enrollment of these individuals as it permits participants and study staff to remain blinded to mutation status. Mutation negative participants will not be exposed to active study drug. However, for each additional drug arm, requirements for participants to know their mutation status may change based on the design (i.e. a drug arm may require a drug treatment for all participants as part of the protocol, such as in a combination therapy approach). Mutation positive participants will be randomized between study drug arms and placebo. The placebo group of mutation positive individuals will be pooled among the treatment groups ("mutation positive placebos"), increasing the statistical power of the study. This use of a pooled placebo group enables a study of more than one therapy to be powered

with fewer total participants and allows more than 50% to be on an active drug, a feature often requested by potential research participants.

Second, families with mutations linked to DIAD are rare and participants typically live at a significant distance from DIAN-TU sites. Because participants typically work and have family responsibilities, there is increased burden of travel and time spent on study activities; however, a high level of participant retention is essential for the success of the study. Therefore, participants who reside outside a reasonable distance from their "host" trial site will be asked to travel to the site only when needed for highly specialized assessments (e.g., PET scans, lumbar puncture (LP), and specialized cognitive testing; these occur at least annually). Regular visits (e.g., for administration of study drugs) may be performed by trial-designated and Good Clinical Practice (GCP) trained home health nurses or other trial-identified satellite sites. For relevant study drug arms, the 3T safety MRIs that are not part of an Annual Visit may be performed at either the participant's host DIAN-TU site or a trial-identified location qualified for the study near the participant's home. For all study drug arms, the annual MRI session will be performed at a DIAN-TU site.

Further, this platform study design allows for flexibility and for the application of an "adaptive design" for which study drug is used. For example, if a study drug failed early due to adverse events or lack of efficacy, a new compound could be added to the same protocol and new participants could be randomized to the actively enrolling study drug arms or a CRI period may open for recruitment.

A more traditional study design with separate biomarker and cognitive endpoints would be extremely difficult in this cohort for two reasons: 1) The participant pool is very limited as families with DIAD causing mutations are rare; and 2) A prolonged treatment period (≥ 4 years in this study) may be needed to determine if the study drugs can slow or prevent cognitive changes in an asymptomatic cohort. The inclusion of these cognitively normal participants is very important, as they may be most likely to benefit from disease-modifying treatments.

However, the subtle cognitive change in the asymptomatic mutation carriers limits the power to detect treatment effects when there are small numbers of participants enrolled. One method to improve the power to detect treatment effects is to include additional control participants. The DIAN Observational study (DIAN-OBS) has been following nearly the same protocol as DIAN-TU-001 to study the natural history of disease progression in DIAD. Given the similarities of the protocol and the fact that the DIAN-OBS study has contributed a significant proportion of the participants to the DIAN-TU-001, data will continue to be used from DIAN-OBS participants who meet the inclusion criteria for DIAN-TU-001 to track disease progression, regardless of the specific therapy being tested. The DIAN-OBS data will be used as additional control participants and will be utilized as a control group to improve power.

Cognitive Run-in Period to Establish Trial-Ready Cohort

A CRI period may be opened prior to randomization into drug arms added to the platform trial. To determine the potential benefits for statistical power, a detailed simulation analyses was

conducted in three study cohorts at risk for AD. Across all datasets, including slopes and intercepts from pre-randomization periods as covariates resulted in the largest increases in statistical power for a 4-year simulated trial. Statistical power increased by 5-11% depending upon randomization scenarios (3:1, 1:1) and the length of the pre-randomization period. In addition, the use of pre-randomization cognitive testing will align the DIAN-TU with ongoing initiatives — the Trial Ready Cohort (TRC) for preclinical/prodromal AD (PAD) trials (TRC-PAD; NCT03638583) and the European Prevention of Alzheimer Dementia Longitudinal Cohort Study (EPAD LCS; NCT02804789) — that are developing trial-ready populations for AD prevention trials (Aisen et al., 2016).

The CRI period will also allow participants that do not currently qualify for DIAN-TU-001 studies (e.g., more than 10 years younger [> −10] than estimated years at symptom onset) to contribute to the understanding of patterns of cognition at the earliest stages of the disease providing scientific contributions. With the development of primary prevention studies in DIAN-TU (US NIH Grant U01AG059798, PI EM McDade), defined as studies in a population at risk for DIAD but known to be mostly free of any detectable pathology at trial entry, there is a strong interest in establishing a trial ready cohort to accelerate recruitment into the therapeutic trial once launched. Furthermore, it also allows at-risk persons that have not yet participated in the DIAN network to experience one component of the clinical trial process. This can help to identify those participants unlikely to be able to stay in a long prevention trial if they are able to start CRI but not continue. These latter two considerations help with trial efficiency.

For further rationale, see Section 1.4.

3.3 Number of Participants and Sites

Individuals will be recruited by host DIAN-TU sites and may also come from other sources such as referring partner sites, and the DIAN-EXR. DIAN-TU sites are located globally. The number of sites and locations may be expanded over the course of the study.

Recruitment of mutation positive participants is with baseline CDR 0 to 1 (inclusive). Mutation positive groups (active vs. placebo) will be enrolled to meet the respective enrollment numbers of asymptomatic (CDR 0) and symptomatic (CDR > 0) participants.

For the gantenerumab and solanezumab arms, a total of 193 participants were enrolled into the double-blind period (144 mutation carriers and 49 mutation non-carriers) with 52 mutation carriers on active gantenerumab, 52 mutation carriers on active solanezumab, and 40 mutation carriers in the pooled placebo arm.

The CRI period may recruit up to 740 participants during any time where a drug arm is not actively randomizing to meet the enrollment required for the three tau-targeted drug arms slated for secondary prevention enrollment (Tau NexGen) and the drug arm(s) slated for primary prevention. Up to 500 participants between 10 years younger than their estimated years to symptom onset (EYO) and 10 years after estimated symptom onset (−10 and + 10 EYO) may be

enrolled in the CRI period if no study drug arm is available for immediate enrollment into DIAN-TU-001, or if a future study drug arm is stopped prior to the planned completion (e.g., at biomarker interim, drug toxicity), to ensure that a sufficient number of active and eligible participants qualify for entry into a drug arm once opened for randomization. In addition, up to 240 participants may be enrolled in the CRI period to establish a trial-ready cohort of participants who are 11 to 25 years younger than their estimated symptom onset (EYO −25 to −11) and are at least 18 years old and cognitively normal (CDR 0) (primary prevention population).

See drug specific appendices for specific enrollment numbers of participants. The number of DIAN-TU sites is estimated to be approximately 40 sites globally. The CRI Entry visit, baseline study visit (V2) and annual visits for the CRI period and/or treatment period will be conducted at the DIAN-TU site. Other visits (e.g., visits for dispensing/administration of study drugs and cognitive testing) may be performed at the DIAN-TU site or by trial-designated and GCP trained home health nurses or other trial-identified satellite sites. For relevant study drug arms, regular interval 3T safety MRIs will be performed at either the host DIAN-TU site or a trial-identified location qualified for the study near the participant's home. Whenever possible, satellite sites for imaging in the US will be sites in the Alzheimer's Disease Cooperative Study (ADCS) and/or Alzheimer's Disease Neuroimaging Initiative (ADNI) that have experience with AD imaging, assessment and therapeutic trials, and have been qualified by the trial's MRI central reader. Preliminary studies suggest that >70% of potential US participants live within a 2-hour drive of an ADCS and/or ADNI site, so we anticipate the majority of scans will be performed at these sites. When other sites are needed, satellite imaging sites that are able to complete and upload safety scans will be individually selected and qualified (Section 6.1.16).

3.4 Participant Enrollment and Randomization

Participants will be recruited from or may be referred to a DIAN-TU site for screening. The complexity of the study and the likelihood that many participants may live at a distance from the DIAN-TU site create additional challenges for enrollment. Individuals interested in the study will be provided with an informed consent form (ICF) for review.

The participant's personal information will be used to create the Globally Unique Identifier (GUID), which consists of random characters. Once the GUID is created, qualified researchers can use it to link an individual's research data across studies, including DIAN-OBS, DIAN-EXR and future studies, without using identifying personal information.

If more than one study drug arm is enrolling, a main ICF will provide detailed information on study design, number and timing of visits and procedures, and the rationale for use of drugs targeting AD pathology. The main ICF will provide information on the route of administration, potential side effects associated with drugs that target Aβ or tau, and study procedures. The ICF will explain that participants will be assigned randomly to an eligible study drug arm and if more than one of the study drug arms is recruiting simultaneously, they will not be able to

choose a specific study drug arm. If only one drug is enrolling, one ICF may be utilized. Local regulations and ethics committee requirements must be followed and may require alternate consent structure and/or practices.

For participants enrolling into the CRI period, an ICF specific to the CRI period will be used. The CRI ICF will provide detailed information on study design, duration, number and timing of visits, procedures, and potential side effects associated with drugs that target amyloid-beta or tau, and intent for participants to enroll in a study drug arm when one becomes available. It will also include the main requirements of future potential drug arm(s) (e.g., duration and frequency of procedures). The CRI ICF will explain that participants who continue to meet eligibility criteria may be randomized to a study drug arm once a drug arm is open. The ICF should be clear that there is the potential to be excluded from the study drug arm if any entry criteria are not met, and it is in the best interest of the participant not to participate. Participants will be re-consented prior to randomization to a study drug arm.

Participants (and their legally authorized representative if the participant is cognitively impaired) will review the ICF and discuss with study staff on the phone or in-person. The participant and/or representative will only sign the ICF after all questions have been answered. The study partner will be provided with information on their role in the study and will sign the ICF; this may be part of the main ICF or a separate ICF, as required by local regulations.

If enrolling directly into a study drug arm, after informed consent is obtained, each participant will be assigned a unique study number and screening visit (V1) procedures will be completed either in the participant's home by a home health nurse, other trial-identified satellite site, or at the DIAN-TU site. Appropriate documentation of informed consent and screening assessments will be monitored by the sponsor and/or sponsor designee. The baseline visit (V2) at the DIAN-TU site will be scheduled 2 to 8 weeks after completion of the screening visit procedures, and **no earlier than 6 weeks after the genetics blood collection, unless the participant enrolled in CRI and genetic testing was completed**. After all baseline measures have been completed, and adherence to inclusion and exclusion criteria has been verified, the participant will be randomized to a study drug arm via the Interactive Web Response System (IWRS). The participant and study staff at the site will know which study drug arm the participant was assigned but will not know whether the participant was assigned to active drug or placebo. If more than one study drug arm is enrolling participants, the participant will review a supplemental drug-specific ICF for the assigned study drug arm that provides additional details of the frequency of side effects and risk/benefit information for that specific study drug.

Participants will receive their first dose of study drug after all visit procedures have been completed and the participant has been randomized and/or assigned treatment per the IWRS. If a participant decides not to continue in the assigned study drug arm after randomization but prior to dosing, they will be withdrawn from the study and may not be re-randomized to a different study drug arm.

See details about participant randomization in each drug-specific appendix.

If enrolling into the CRI period, after informed consent is obtained, each participant will be assigned a unique study number and CRI screening visit (CRI Screen) procedures will be completed in the participant's home, other trial-identified satellite site, or at the DIAN-TU site. Once a new study drug arm(s) is open, participants will have a screening visit (V1) conducted either in their home by a home health nurse, or at the DIAN-TU site to collect safety labs and to reassess the suitability of the participant for entry into the new study drug arm(s).

If enrolling into an OLE period, a separate consent will be obtained, which will be available at the time of OLE enrollment.

3.5 Measured Study Endpoints

The biomarker endpoints used for the interim biomarker analyses are specific for each drug based on mechanism of action. These are listed in each drug-specific appendix and/or drug-specific SAP appendix. The designation of primary, secondary, and exploratory endpoints are also specific for each drug and are listed in the drug-specific appendices and/or drug-specific SAP appendices.

Note – measures and endpoints for completed drug arms can be found in prior protocol amendments and SAPs; the gantenerumab open label extension endpoints are in Appendix 3. The E2814 measures and endpoints with concurrent lecanemab treatment are in Appendix 4.

Additional outcome measures include comparisons between each drug and placebos and eligible DIAN-OBS participants for measures listed below if/as specified in the drug-specific SAP appendix.

Clinical Measures

Clinical measures to be obtained at the CRI Entry, baseline (V2), and annual visits for both the CRI period and treatment periods will be administered at a DIAN-TU site include:

- Clinical Dementia Rating™ (CDR), including Clinical Dementia Rating Sum of Boxes™ (CDR-SB) and clinician's diagnostic assessment
- Geriatric Depression Scale (GDS)
- Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Functional Assessment Scale (FAS)
- Mini-Mental State Examination (MMSE)*

*In addition, the MMSE will be administered at the site or via home visits for secondary prevention population only by a DIAN-TU certified rater at the 26-week visit in between the annual visits, as specified in the CRI and drug-specific appendices.

Cognitive Measures

Cognitive batteries are defined in respective arm-specific appendices. Refer to the arm-specific *DIAN Trials Unit Cognition Core Procedures Manuals* for additional information. Refer to prior

amendments for details on the cognitive battery administered in completed or closed drug arm periods.

Cognitive Battery for Gantenerumab Open-Label Extension Period

Cognitive measures collected in gantenerumab and solanezumab double-blind period, and continued into the gantenerumab open-label extension (OLE) period, are listed below and include the iPad-administered and conventional cognitive (pen/paper) tests. Refer to Section 6.1.14.1 for the frequency of the assessments in the gantenerumab OLE and the drug-specific appendix (Appendix 3) for detailed visit numbers and timing. Testing is administered at a DIAN-TU site and/or via home health nurse certified raters.

iPad-administered Cognitive Testing:

- International Shopping List Test (12-Item Word List Learning): 3 learning trials, Immediate Recall, 30-min Delayed Recall (Cogstate)
- Groton Maze Learning Test: Timed Chase Task, 5 learning Trials, Immediate Recall, 30-min Delayed/Reversed Recall (Cogstate)
- Cogstate Detection Task
- Cogstate Identification Task
- Cogstate One Card Learning Test
- Cogstate One-Back Task
- Behavioral Pattern Separation Object Task
- Memory Complaint Questionnaire (MAC-Q)

Conventional Cognitive Testing (Pen/Paper):

- Trailmaking Test parts A & B
- Wechsler Memory Scale-Revised (WMS-R) Digit Spatial Span Forward and Backward
- Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit-Symbol Substitution Test
- Raven's Progressive Matrices (Set A)
- Category Fluency (Animals & Vegetables)
- WMS-R Logical Memory/Paragraph Memory (Immediate & Delayed Recall)

DIAN-TU Harmonized Cognitive Battery for Cognitive Run-In (CRI) Period and Tau Drug Arms

Cognitive measures collected in the CRI period and tau drug arms are administered at regular intervals as directed in the arm-specific appendix by a trial-certified cognitive rater, at either a DIAN-TU site or via home health nurse, and include the below cognitive battery harmonized with the DIAN Observational (DIAN-OBS) study and primary prevention treatment protocol (DIAN-TU-002). Refer to the CRI appendix (Appendix 1) and E2814 appendix (Appendix 4) for detailed visit numbers and timing.

- MAC-Q
- Buschke and Grober Free and Cued Selective Reminding Test-Immediate Recall (FCSRT-IR)

- WMS-R Logical Memory/Paragraph Memory (Immediate & Delayed Recall), Alternate Paragraph for Logical Memory I & II – Version A (Immediate and Delayed) and Alternate Paragraph for Logical Memory I & II – Version B (Immediate and Delayed)
- Category Fluency (Animals)
- WAIS-R Digit-Symbol Substitution Test
- Trailmaking Test Parts A & B
- WMS-R Digit Spatial Span Forward and Backward)

Smartphone-based cognitive assessments will be administered to participants in the CRI period and/or randomized to an enrolling study drug arm using a mobile phone application, Ambulatory Research in Cognition (ARC). These tests will include measures of episodic memory, attentional control, and processing speed. These assessments will be self-administered by the participants on their personal smartphones. If participants do not own a smartphone or their device does not meet minimum specifications, a study phone will be provided.

Compliance with the smartphone-based cognitive measures is considered exploratory and non-participation will not be considered reason for discontinuation in the study and will not be considered protocol deviations. Based on operational and regulatory considerations, the study sponsor will determine which sites will administer smartphone-based cognitive assessments, with the explicit goal of full site participation.

Participants will complete ARC assessments at regular intervals as specified in the drug-specific appendix.

Imaging Biomarker Measures:

The following imaging endpoints may be assessed in any period or study drug arm, as specified in the protocol appendices. Refer to the final drug-specific SAP appendix for differentiation of endpoint classification based on the respective drug's target and mechanism of action.

- Amyloid load based on imaging with [^{11}C]PiB-PET
- FDG-PET metabolism
- Change in Tau PET measures of neurofibrillary tangle (NFT) burden
- Clinical MRI features such as microhemorrhages (MCH), white matter hyperintensities (WMH), cerebral infarction, and amyloid-related imaging abnormality (ARIA).
- Functional Connectivity MRI measures (fc-MRI)
- Diffusion Tensor Imaging (DTI) MRI, including diffusion basis spectrum imaging (DBSI)
- Blood flow measures by Arterial Spin Labeling (ASL) MRI
- Brain atrophy as measured by structural MRI (volumetric MRI)
- Novel MRI quantitation techniques of neurodegeneration or AD
- Novel PET quantitation techniques of neurodegeneration or AD

Fluid Biomarker Measures:

The following biomarker endpoints may be assessed in any period or study drug arm, as specified in the protocol appendices. Refer to the final drug-specific SAP appendix for differentiation of endpoint classification based on the respective drug's target and mechanism of action.

- CSF amyloid-beta species
- CSF tau species (including ptau)
- CSF NfL and measures of neurodegeneration
- Blood amyloid-beta species
- Blood tau species (including ptau)
- Blood NfL and measures of neurodegeneration
- Other CSF biomarkers of AD
- Other blood biomarkers of AD

Additional Measures:

- Genetic, epigenetic, or genomic analyses of co-factors for rate of progression and response to treatment.
- Additional genetic analyses that may be done include whole genome sequencing, RNA transcripts (cells and extracellular vesicles), bulk RNAseq, and single cell RNAseq
- Other drug-specific biomarkers, as specified in each drug-specific appendix

Additional secondary measures may be listed in each drug-specific appendix. Refer to the final SAP for drug-specific differentiation of endpoint classification based on the respective drug's target and mechanism of action.

3.6 Safety Endpoints

This study will assess safety and tolerability in individuals at risk for dominantly inherited AD. Safety endpoints used will be the incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and treatment discontinuations. Analysis will be on an intent-to-treat basis. Clinical laboratory evaluations, vital signs, and 12-lead ECGs will also be measured throughout the study.

Amyloid-related imaging abnormalities (ARIA) measures are a safety endpoint in studies of amyloid removing drugs. Based on the assigned study drug arm, periodic MRI scans may assess for ARIA changes. ARIA can occur as either cerebral edema (ARIA-E) or as hemorrhages (ARIA-H), typically microhemorrhages, but larger hemorrhages and frank infarction have also been reported (Sperling, Salloway et al. 2012). MRI scans will be analyzed for ARIA changes at the Mayo Clinic Aging and Dementia Imaging Research (Mayo-ADIR). The number of microhemorrhages (ARIA-H, including both hemorrhages and hemosiderin deposits) and size of areas of edema (ARIA-E) will be monitored at entry and throughout the trial. Incidence of ARIA and comparison to placebo will be made.

A report of new ARIA changes in a participant will trigger a review by the DIAN-TU Medical Director or designee, Project Arm Leader (PAL), and site principal investigator. This review will include contact with the participant or caregiver to assess for any symptoms associated with the changes and discussion with the central readers. The PAL, as a site independent clinician, will help ensure consistency of decisions within a study drug arm across sites during the study. See each drug-specific appendix for drug-specific ARIA algorithms. The DIAN-TU Medical Director will ensure consistency across study drug arms and will have final decision-making authority on changes in dosing of study drug or safety monitoring; this decision should be received by the site within 7 days of the report of the new ARIA changes, but no later than the day prior to the planned administration of the next dose of medication. A similar process will be followed if a follow-up MRI shows worsening of a previously reported ARIA.

Additional assessments based on drug-specific safety concerns are detailed in each drug-specific appendix (Appendix 3 for gantenerumab and Appendix 4 for E2814).

An independent Data Safety Monitoring Board (DSMB) will assess safety data periodically throughout the study. The DSMB will have timely access to data, including clinical laboratory values, ECGs, MRI results, and clinical and cognitive testing scores; this will include access to unblinded data when requested. The DSMB will monitor the incidence of ARIA and comparison to placebo. See Section 7.10 and the DSMB charter for additional information.

3.7 Study Schedule

The schedule of visits, including drug-specific tests and frequency for each drug, is provided in each appendix.

3.8 Total Study Duration and Duration of Treatment

The total study duration depends on the time in CRI, the duration of each drug arm, and any extensions or OLE for the associated drug arm. For drug arms utilizing a common-close design, the treatment duration of each study drug arm may vary depending on the duration of enrollment and the treatment time needed for the study drug to achieve its goal. A study drug arm may be stopped early or revised (e.g., dose adjustment or treatment duration), based upon the results of the interim analyses or information from other clinical trials for the same drug, as outlined in each drug-specific appendix.

Participants in double-blind periods will continue to receive blinded treatment until **the last participant** enrolled completes the randomized period of treatment or withdraws (“common close”). Based on the time required for full recruitment, the total duration may vary from 48 to 80 months. For example, participants enrolled in the first month may receive treatment for approximately 72 months (if recruitment takes 24 months + 48 months of treatment); for those enrolled in the last month, the duration of treatment would be 48 months.

If the CRI period is open to enrollment, a CRI period may last until a study drug arm opens for randomization, but no longer than approximately 3 years. If a participant is participating in a CRI period, a minimum of 8 weeks must elapse between the participant's last administration of the cognitive battery during the CRI period and administration of the baseline (V2) cognitive battery of a treatment arm.

Once a decision is made for an OLE of a study drug arm, participants may be eligible to continue or start treatment in an open-label extension period (Section 3.9) if the study drug arm demonstrates potential clinical or cognitive benefit.

Details regarding study duration and duration of treatment are described in the CRI and drug-specific appendices in Appendix 1, Appendix 3, and Appendix 4.

3.9 Open-label Extension

Upon completion of the double-blind treatment period for each study drug arm (i.e., last enrolled participant has completed), an open-label extension (OLE) period may be initiated for drugs that demonstrate a potential for clinical benefit, with approval from the sponsor. In the OLE period, participants may be eligible to receive active study drug for an additional treatment period as specified in the drug-specific appendices.

Only DIAD mutation positive participants will be eligible for an OLE period; mutation negative participants (non-carriers) will be excluded. Participants who do not want to know their mutation status will not be eligible. Further details are outlined in Section 6.3.6. Participants are encouraged to proceed with genetic counseling, at a minimum, in preparation for disclosure of DIAD mutations, before the end of the double-blind treatment phase to enable more rapid entry into the OLE. Consent forms for OLE periods will be available towards the timeframe when an OLE is planned to commence.

All OLE participants and study sites will be kept blinded to prior drug assignment until the end of the OLE period to protect study integrity.

For drug arms that demonstrate potential for clinical benefit, participants from a concurrent negative drug arm(s) may have the option of enrolling into an open OLE period after the drug-specific washout period from their last double-blind dose.

Participants entering the OLE will follow the drug-specific schedule of visits for the OLE in each drug-specific appendix.

Access to study drug may be terminated if any of the following occur: a) the study drug arm is terminated due to lack of efficacy and/or safety concerns; b) the medication is commercially available in the country where the participant lives, i.e., the participant can obtain medication from a government sponsored or private health program; or c) therapeutic alternatives become available in the local market. Furthermore, the sponsor can terminate the OLE at any time for any reason.

4 STUDY POPULATION AND SITES

It is anticipated that participants eligible for the CRI period will also meet entry criteria at baseline (V2). However, it is possible that a participant enrolled in the CRI period will not meet entry criteria at baseline (V2). Any entry criteria for which the participant no longer qualifies for at baseline (V2) will be assessed and reviewed by the DIAN-TU Medical Director to determine if entry into a study drug arm is appropriate.

The following inclusion and exclusion criteria do not apply to OLE periods; eligibility criteria for OLE period are presented in the respective drug-specific appendices (e.g. in Appendix 3 for gantenerumab).

4.1 Inclusion Criteria

A participant may be included in the CRI period or double-blind periods active as of this amendment if the following Inclusion Criteria are met:

1. Written informed consent is signed and dated by the participant, study partner (if applicable) and/or by the participant's legally authorized representative according to local regulations for the core trial ICF and, if applicable, the CRI ICF and/or the drug-specific ICFs.
2. Participant is 18 to 80 years of age (inclusive).
3. People of childbearing potential (POCBP), if partner is not sterilized, must agree to use highly effective contraceptive measures (e.g., hormonal contraception, intra-uterine device, sexual abstinence, vasectomized partner) from screening (V1) until five (5) half-lives after last dose of any study drug. Refer to the *Global Manual of Operations* for acceptable methods of contraception.
4. Mutation status (*must fulfill criteria a or b, based on estimated years from symptom onset [EYO])*:
    a. −10 to +10 EYO (secondary prevention population):
        i. Participant is a carrier[2] of a mutation in *PSEN1*, *APP* or *PSEN2* gene that is associated with dominantly inherited Alzheimer's disease[3] OR, when allowed for individual arms, at 50% risk for such a mutation (e.g., does not know their

[2] Mutation genotype will be determined at the trial-designated CLIA-approved lab as part of the screening process. Results of this testing will not be available to the DIAN-TU site or to the participant. Participants who ask to be informed of the test results will be referred for genetic counseling and will have testing ordered through a clinical laboratory; results will be sent to the genetic counselor who will disclose results to the participant. Note that participants who become aware that they are mutation negative will be excluded from the study.

[3] The sponsor will provide a list of mutations that are judged to be associated with dominantly inherited Alzheimer's disease. Site staff should confirm that the mutation in each potential participant's family is on the current mutation list.

mutation status AND is a child or sibling of known mutation carrier). ***Note****: Participants who are aware that they are mutation negative are not eligible for enrollment.*

ii. Participant is within −10 to +10 years (inclusive) of the predicted (parental or mutation) or actual (participant) age at cognitive symptom onset. The predicted age at onset is determined based on their mutation type or family pedigree (refer to *Global Manual of Operations* for calculation of estimated age at onset).

b. −25 to −11 EYO (primary prevention population):

i. Participant is a carrier[2] of a mutation in *PSEN1*, *APP* or *PSEN2* gene that is associated with dominantly inherited Alzheimer's disease[3] OR does not know their mutation status AND there is a mutation in their family pedigree)

ii. Participant is between −25 to −11 years from predicted age of cognitive symptom onset based on their mutation type or family pedigree (refer to *Global Manual of Operations* for calculation of estimated age at onset).

Note*: If the at-risk parent is deemed a non-carrier at any time during the study, the participant will be withdrawn*

5. Cognitive status *must fulfill criteria a or b, based on EYO*:
   a. −10 to +10 EYO (secondary prevention population): Cognitively normal or with mild cognitive impairment or mild dementia, CDR 0 to 1 (inclusive).
   b. −25 to −11 EYO (primary prevention population): Cognitively normal (CDR 0).
6. Fluency in DIAN-TU trial approved language and evidence of adequate premorbid intellectual functioning. Participants must be fluent in languages for which cognitive and clinical measures have been translated and validated for use in the DIAN-TU. Fluency is generally defined as daily or frequent functional use of a language generally from birth or a young age. In cultures where multiple languages are spoken or for participants who are multilingual, determination as to whether a participant's level of fluency in languages for which clinical and cognitive measures are available meets qualification for the study should be made by the site principal investigator.
7. Adequate visual and auditory abilities to perform all aspects of the cognitive and functional assessments.
8. Receiving stable doses of medication(s) for the treatment of non-excluded medical condition(s) for at least 30 days prior to CRI Entry visit and baseline visit (V2) with the exception of medications taken for episodic conditions (e.g., migraine abortive therapy, antibiotics and other medications for upper respiratory and gastrointestinal ailments), AND, if treated with cholinesterase inhibitors and/or memantine, all of the following conditions are also met:

a. The participant has been taking these medications for at least 90 days prior to CRI Entry visit and baseline visit (V2) and has been on a stable dose for at least 2 months (60 days) prior to CRI Entry visit and baseline visit (V2).
b. The participant is free of any clinically important side effects attributable to the drug. Side effects that are intermittent, stable or well-tolerated by the participant are not exclusionary.

9. Has a study partner who in the investigator's judgment is able to provide accurate information as to the participant's cognitive and functional abilities, who agrees to provide information at the study visits that require study partner input for scale completion, and who signs the necessary informed consent form, if applicable.
10. Agrees not to donate blood or blood products for transfusion from screening (V1) for a study drug arm for the duration of the study and for one year after the final dose of study drug. Donation of blood or blood products for transfusion is allowed during the CRI period.
11. In the opinion of the investigator, the participant will be compliant and have a high probability of completing the study.
12. Willing to complete all study-related testing, evaluations, and procedures.

4.2 Exclusion Criteria

A participant will be excluded from the double-blind period if <u>any</u> of the following Exclusion Criteria are met. Refer to the drug-specific appendix for any additional drug-specific exclusion criteria outlined in the baseline visit (V2) assessments.

CNS Disorders

1. Significant neurologic disease (other than AD) or psychiatric disease that may ***currently or during the course of the study*** affect cognition or participant's ability to complete the study. This may include clinically significant disorders such as: recent or severe head trauma causing cognitive change, uncontrolled seizure disorder, non-AD neurodegenerative disease, hydrocephalus, cerebral/spinal hematoma, CNS infection (e.g., encephalitis or meningitis), neoplasm, toxic exposure, metabolic disorder (including hypoxic or hypoglycemic episodes) or endocrine disorder; psychiatric disorders such as schizophrenia, schizoaffective disorder, bipolar disorder or major depression, or any other psychiatric condition/disorder which could significantly interfere with the participant's cooperative participation (e.g., prominent anxiety, agitation or behavioral problems). **Disorders that are controlled medically or remote history of these disorders (e.g., history of febrile seizures in childhood) that are not likely to interfere with cognitive function and compliance with study procedures are not exclusionary**.

2. At high risk for suicide, e.g., significant suicidal ideation or attempt within last 12 months, current major depression (as defined in DSM-V), or increased suicide risk based on CRI Entry visit or screening (V1) C-SSRS. Current stable mild depression or current use of antidepressant medications is not exclusionary.
3. History of clinically evident stroke or history of clinically important carotid or vertebrobasilar stenosis, plaque, or other prominent risk factor for stroke or cerebral hemorrhage (including atrial fibrillation and required anticoagulation, documented transient ischemic attack [TIA] in the last 12 months). Low dose aspirin (≤ 325 mg daily) is not exclusionary.
4. Alcohol or substance use sufficient to meet DSM-V criteria currently or within the past 1 year.

Imaging-related Exclusion Criteria:

5. History of brain MRI scan indicative of any other significant abnormality, history or evidence of a single prior hemorrhage >1 cm^3, 2 or more subcortical infarcts, evidence of a single prior cortical infarct >1 cm^3, evidence of a cerebral contusion, encephalomalacia, aneurysms, vascular malformations, subdural hematoma, or space-occupying lesions (e.g., large arachnoid cysts or brain tumors, such as meningioma), hydrocephalus (other than hydrocephalus ex vacuo). Minor or clinically insignificant imaging findings are not exclusionary.

   ***Note**: For participants who have participated in the DIAN Observational study, site staff should work with DIAN Observational Imaging Core to review results of MRIs done in the observational study so that those with preexisting exclusionary findings on MRI are not unnecessarily subjected to CRI Screen or screening (V1) and CRI Entry or baseline (V2) visit procedures.*
6. Presence of certain implanted medical devices, such as some pacemakers, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin or body which would preclude MRI scan.
7. For male participants that may be exposed to [^{18}F]MK-6240 PET scan:
   a. Male participants with female partners who are pregnant or of childbearing potential must agree to refrain from sexual activity for 24 hours following administration of [^{18}F]MK-6240 injection.
   b. Additionally, males must agree not to donate sperm for 24 hours following administration of [^{18}F]MK-6240 injection.

Cardiovascular Disorders

8. Uncontrolled hypertension within 6 months prior to CRI Screen visit or screening (V1) (e.g., sustained systolic BP $>$ 160 mm Hg or diastolic BP $>$ 95 mm Hg).

9. Myocardial infarction or other myocardial ischemic events within the last 2 years.
10. Heart failure that results in limitation of physical activity (e.g., New York Heart Association [NYHA] functional classification stage 2 or higher).
11. History of atrial fibrillation unless more than one year ago, and no structural lesions (e.g., atrial enlargement or cardiomyopathy) that would increase risk of stroke.
12. 12-lead ECG: Clinically significant abnormalities including Bazett's QTc interval greater than 450 msec for males and 470 msec for females; in participants above 65 years of age: 470 msec (AV-block I° allowed; RBBB allowed). Site principal investigator or designated sub-investigator will be responsible for initial read on ECGs done at CRI Entry and baseline (V2). In the event that the central read becomes available after study drug is dispensed/administered and is exclusionary when the local read was not, the site principal investigator or designated sub-investigator, in consultation with the Project Arm Leader and Medical Director or designee, will decide if the participant should continue in the study. A discrepancy between the local and central read will not be considered a protocol deviation. When there are differences in ECG interpretation between the investigator and the cardiologist at the central ECG laboratory, the investigator's interpretation will be used for study entry and immediate participant management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

Hepatic / Renal Disorders

13. Alanine aminotransferase (ALT) ≥ 2 times the upper limit of normal or aspartate aminotransferase (AST) ≥ 3 times the upper limit of normal or total bilirubin ≥ 2 times the upper limit of normal.
14. Creatinine clearance lower than 30 mL/min according to Cockcroft-Gault formula (if confirmed at re-test).
15. Clinically significant abnormalities in urinalysis.

Infections/Immune Disorders

16. History of HIV infection, history of Hepatitis B infection within the past year, history of Hepatitis C infection which has not been adequately treated or history of spirochete infection of the central nervous system (CNS), (e.g., syphilis, Lyme or borreliosis).
17. Known allergies, hypersensitivity, intolerance to study drug or its excipients (see current Investigator's Brochures) or sensitivity to study-drug specific PET imaging agents.
18. Treatment with immunosuppressive medications (e.g., systemic corticosteroids) within 90 days prior to the CRI Entry visit and baseline (V2) visit (topical and nasal corticosteroids and inhaled corticosteroids for asthma are permitted) or chemotherapeutic agents for malignancy within the last 3 years.

Metabolic/Endocrine Disorders

19. Current clinically significant abnormalities of thyroid function studies, clinically significant deficiency in B_{12}. B_{12} less than the lower limits of normal with normal methylmalonic acid (MMA)/homocysteine is not deemed clinically significant, therefore not exclusionary[4].
20. HbA1c >8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes). Participants may be rescreened after 3 months to allow optimization of diabetic control.
21. Morbid obesity with significant comorbidities or that would preclude MRI imaging.

Co-Medications

22. Current chronic use of anticoagulants (e.g., warfarin, dabigatran, rivaroxaban or apixaban) or of clopidogrel is exclusionary. Limited (occasional or isolated) use of anticoagulants / antiplatelet compounds in cases such as surgical procedures, as well as daily use of low dose (≤ 325 mg) aspirin is not exclusionary.
23. Have been exposed to a monoclonal antibody targeting beta amyloid peptide within the past six months, or five half-lives from screening visit (V1), whichever is longer.
24. Received any other investigational treatment within 3 months or 5 half-lives of CRI Screen and screening visit (V1), whichever is longer.

***Note**: Use of some treatments for AD and other medications may be permitted in this study in accordance with the guidelines in Concomitant Medications, Section 5.3.*

Other

25. Lack of sufficient venous access.
26. Clinically relevant abnormalities in hematology, coagulation studies or clinical chemistry.
27. History of cancer within the last 5 years, except basal cell carcinoma, non-squamous skin carcinoma, prostate cancer or carcinoma in situ with no significant progression over the past 2 years.
28. Any other medical condition that could be expected to progress, recur, or change to such an extent that it could bias the assessment of the clinical or mental status of the participant to a significant degree or put the participant at special risk.

[4] If B_{12} is less than the lower limits of normal, a follow-up test of MMA and/or homocysteine should be performed to assess MMA/homocysteine

29. Currently, or within the last month prior to CRI Screen or screening (V1), participated in a clinical trial including a nonpharmacological trial with a key objective of improving cognition.
30. Positive urine or serum pregnancy test or plans or desires to become pregnant during the course of the trial.
31. Currently breastfeeding. Participants must agree to refrain from breastfeeding during their participation in the trial and until 5 half-lives after the last dose of any study drug.
32. Unable to complete CRI Entry visit or baseline visit (V2) procedures with appropriate cognitive and clinical scores for eligibility (e.g., mild dementia).

4.3 Participant Recruitment and Screening

This study will recruit participants from the DIAN Observational study, DIAN-TU sites, DIAN-TU partner sites, DIAN-EXR, and families identified by the sites. These individuals will be recruited by and/or referred to a DIAN-TU site for screening. A list of screening labs and assessments for the CRI period is included in Section 6.3.1 and a list of screening labs and assessments for the double-blind treatment period is included in Section 6.3.2**.**

4.4 Discontinuation/Early Withdrawal of Participants

4.4.1 Criteria for Discontinuation

Participants could be discontinued from the double-blind period or OLE for any of the following reasons; discontinuation criteria for individual drug arms may also be specified in the drug-specific appendices:

1. Participants would be discontinued from this study if they were involved in any other clinical trial or other research judged not to be scientifically or medically compatible with this study. Participation in any other concurrent clinical trial that studies an investigational drug or any procedures to improve cognition is not permitted.
2. Site principal investigator, Project Arm Leader (PAL), and Medical Director or designee decides participant should be discontinued, e.g., after an SAE or other clinically significant event or laboratory finding. Refer to drug-specific appendices for any drug-specific discontinuation criteria related to adverse events and laboratory findings.
3. Participant or participant research proxy (if participant is cognitively impaired and unable to provide their own consent) decides to withdraw consent, including declining to consent to any protocol amendments.
4. Participant becomes pregnant.
5. Participant non-compliance, based on decision of site study staff or Medical Director. Determination of non-compliance would not apply to doses that are missed or reduced

when the site principal investigator/sub-I, PAL, and Medical Director or designee decide that changes in study drug dosing are necessary for medical or safety reasons. During the CRI period, participants who miss more than two consecutive visits should be evaluated for continued suitability in the trial by the principal investigator/sub-investigator, PAL, and Medical Director or designee.

6. Participant can no longer contribute to the collection of key outcomes data. Thus, a participant who cannot contribute to key endpoints would be discontinued from the double-blind treatment period but eligible for continued clinical and/or cognitive follow-up and/or OLE* (Section 6.3.7).
7. Known negative mutation carrier status or determination that they are no longer at-risk (negative risks status). For example, if a participant enters the study unaware of their mutation status (when allowed), but later learns that they are mutation negative, they would be discontinued from the study.

If a participant discontinues early from a double-blind or OLE treatment period, every effort will be made to complete all study assessments, as applicable, at an Early Termination visit. **These assessments would not be completed for participants who are withdrawn because they become unblinded to genetic status and are found to be mutation negative.**

If a participant discontinues early from the CRI period, no additional testing or termination procedures are required, unless deemed necessary by the sponsor medical monitoring team.

***Post-Treatment Follow-Up Period**: Any participant that discontinues from treatment due to safety reasons or inability to continue treatment and/or key study procedures will be encouraged to continue with any assessments and measures able to be performed based upon the assessment schedule. The assessments will be determined based on discussion with the site principal investigator and sponsor.

4.4.2 Replacement of Participants

Enrollment for each study drug arm will be ongoing until all groups within the study drug arm are filled. Participants may be replaced if they withdraw prior to randomization.

4.5 Transfer of Participants between Sites

A participant may request a transfer to a different DIAN-TU site if they relocate or if transfer to a new site will enable improved compliance with all study visits and procedures. Should the trial be closed at a DIAN-TU site, participants from the closing site would be offered the option of remaining in the study and transferring to another site to complete study procedures.

Participants transferring to another site must continue to be administered the same country-specific language and locally adapted cognitive and clinical assessments as they had been completing at their prior site for consistency in data collection.

Participants may have some study procedures performed at other DIAN-TU sites if the procedure cannot be performed at the DIAN-TU site under which they enrolled (e.g., due to equipment failure or PET tracer availability). These participants would remain enrolled at their original DIAN-TU site.

4.6 Expectations and Withdrawal of Sites

Sites are expected to fulfill all study obligations. DIAN-TU sites that fail to fulfill study obligations may be terminated from the study. While a site is on probationary status or if a site is terminated, participants at that site will be offered the option of transferring to a different DIAN-TU site on a temporary or, if the site is terminated, permanent basis. After obtaining signed release from participants, copies of all source documents should be made available to the new site as rapidly as possible and at least within 30 days after probationary status begins.

5 STUDY DRUGS

See each drug-specific appendix for drug-specific background, preclinical and clinical data, rationale for specific biomarkers endpoints to assess target engagement, risks/benefits and specifics of drug packaging, preparation, administration, compliance, analysis issues, and drug-specific adverse events, and schedule of visits.

The following information on blinding, concomitant medications, and treatment compliance applies to all drugs.

5.1 Blinding

During double-blind periods, participants and study staff will remain blinded as to whether participants are on active drug or placebo. Participants and staff will not be blinded as to the treatment route and interval. The procedures taken to maintain blinding are detailed in each drug-specific appendix and/or associated *DIAN-TU Pharmacy Manual*.

During double-blind periods in which non-carriers are eligible to participate, genetic status will not be disclosed to either the participant or study staff. Mutation positive participants may already be aware of their genetic status and choose to disclose this to study staff. The mutation positive participants will be encouraged not to disclose their genetic status to study staff. For participants who have not been provided with their mutation status, the staff will be encouraged not to make assumptions about genetic status or group assignment within a study drug arm when adverse events (AEs) are reported. Genetic status will be confirmed for entry into any OLE period.

Should any drug arm continue into an open-label extension period, treatment assignment from the double-blind period may remain blinded to investigators and participants based on the goals of the OLE period.

5.2 Breaking the Blind

With the exception of the periodic DSMB data review or required regulatory reporting for expedited reports by designated safety personnel who do not have contact with study staff or participants, the study blind will not be broken until all participants in a blinded study drug arm have completed the double-blind treatment period and the database for that study drug arm is locked. Only in the case of an emergency, when knowledge of the study drug is essential for the immediate clinical management or welfare of a specific participant, may the investigator unblind a participant's treatment assignment.

Prior to any unblinding, the investigator is strongly advised to discuss options with the PAL, Medical Director or designee. As soon as possible, and without revealing the participant's study drug assignment (unless important to the safety of participants remaining in the study), the investigator must notify the sponsor if the blind is broken for any reason and the investigator was unable to contact the sponsor prior to unblinding. The investigator will record in source documentation the date and reason for revealing the blinded treatment assignment for that participant**.**

5.3 Concomitant Medications

All concomitant medication taken during the study must be recorded on the Concomitant Medication electronic case report form (eCRF). Participants will be instructed to consult the investigator or other appropriate study personnel at the site before initiation of any new medications or supplements and before changing dose(s) of any current concomitant medications or supplements.

To approximate standard of care for AD, use of certain approved treatments for AD is permitted in this study, but use of additional anti-amyloid therapies i.e. Aduhelm™ (aducanumab), are exclusionary and may not be used during trial participation. This section provides additional guidance on managing concomitant medication use during the trial. Before starting any Alzheimer's disease medication, participants should be informed to discuss with their site study team, and sites should discuss with the sponsor, to determine if the medication use affects the participant's continued eligibility. Taking a drug that conflicts with the trial design may exclude continued participation, e.g., taking an approved anti-amyloid treatment while participating in an anti-amyloid study treatment arm.

Allowed Medications. Use of the following approved treatments for AD is permitted during the study, provided that such medications have been given for at least 90 days and the dose has been unchanged for 2 months (60 days) before CRI Entry and Visit 2: donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Razadyne®, Razadyne®ER), and memantine (Namenda®). Doses of these medications should remain constant throughout the study.

If a participant has recently stopped acetylcholinesterase inhibitors (AChEIs) and/or memantine, he or she must have discontinued treatment at least 90 days before CRI Entry and

Visit 2. Other vitamins or nutraceuticals given for their possible effects on AD may be continued on stable doses beginning 90 days before CRI Entry and Visit 2.

Starting, stopping, or changing doses of AChEIs and/or memantine during the study might interfere with outcome measures and therefore could result in discontinuation of the participant from the study.

Before a participant starts, stops, or changes doses of AChEIs and/or memantine or other treatments for their AD, the PAL, Medical Director or designee should be contacted to determine whether or not the participant should continue in the study and whether or not clinical outcome measures should be performed. It should be documented if sponsor discussion and approval in advance of starting, stopping, or changing doses is in place prior to any change. Changes may be tracked as a protocol deviation for analysis purposes.

If changes are made without prior contact with the PAL, Medical Director or designee, the principal investigator/sub-investigator, once informed of these changes, should contact the PAL, Medical Director or designee to discuss and jointly determine whether or not the participant should continue in the study and whether or not clinical outcome measures should be performed. It will be a protocol deviation if discussion and sponsor approval prior to the start, stop, or modification of such medications were not in place.

Non-medication treatments for AD such as psychotherapy are permitted but are subject to the same restrictions as medication treatment taken for AD.

Other concomitant medications that affect CNS function may be given if the dose remains unchanged throughout the study. Doses of these compounds should remain constant from 4 weeks before CRI Entry and 4 weeks before baseline (Visit 2).

To avoid effects on cognitive measures, participants should not stop receiving any medications that affect CNS function during the study, add any to the treatment regimen, or change doses of these medications. If unforeseen starting, stopping, or changing of stable doses of these drugs occurs during the study, the PAL, Medical Director or designee must be contacted to determine whether or not the participant should continue in the study and whether or not outcome measures should be performed.

Use of benzodiazepines for treatment on an as-needed basis for insomnia or daily dosing as anxiolytics is permitted. Use of sedatives or hypnotics should be avoided for 8 hours before administration of the cognitive tests unless they are given chronically.

5.4 Treatment Compliance

Compliance will be monitored for all drugs and recorded on study documents. See each drug-specific appendix for specific compliance monitoring for each study drug.

6 STUDY PROCEDURES

The procedure schedule described in this section includes any procedures that may be performed in treatment arms and/or CRI periods. The inclusion of specific procedures and timing for completion are described in the respective protocol appendices.

6.1 Procedures

6.1.1 Participant Informed Consent

Prior to any study procedures or study-related activities, an IRB or IEC approved Informed Consent Form (ICF) must be signed and dated by the participant (and/or caregiver/legally authorized representative if the participant is cognitively impaired) and by the study partner (if required). Study staff must document the informed consent process in the participant's source document. A copy of the signed and dated ICF will be provided to the participant and study partner.

Because of the complexity of this study design, informed consent may occur in two steps when more than one drug is recruiting simultaneously. In addition, a separate informed consent will be obtained for CRI and/or OLE periods.

For participants enrolling into the CRI period, an ICF specific to the CRI period will be used. The CRI ICF will provide detailed information on study design, duration, number and timing of visits and procedures, and potential side effects associated with drugs that target amyloid-β or tau, and intent for participants to enroll in a study drug arm when one becomes available. It will also include the main requirements of future potential drug arm(s) (e.g., duration, frequency of procedures, etc.). The CRI ICF will explain that participants who continue to meet eligibility criteria may be randomized to a study drug arm once a drug arm is open. The ICF should be clear that there is the potential to be excluded from the study drug arm if any entry criteria are not met and it is in the best interest of the participant not to participate. Participants will be re-consented prior to enrollment to a study drug arm.

For participants enrolling into a treatment period when more than one drug arm is enrolling, a main ICF and supplemental drug-specific ICF may both be used. The main ICF will include a description of the overall study including an overview of possible side effects of the study drugs and differences between study procedures for the different study drug arms. Participants signing the main ICF agree to screening and randomization and indicate their intention to enter the study. After randomization, a supplemental study drug arm-specific ICF document may be reviewed with and signed by the participant (and/or caregiver/legally authorized representative if the participant is cognitively impaired). This supplemental ICF will contain additional details about the procedures, risks and benefits of the specific study drug arm. Participants and their caregivers will have the opportunity to review the main and all supplemental ICFs before they sign the main study informed consent. This two-step approach is needed to keep the ICF concise as participants will only be assigned to one study drug arm, and also keeps confidential

drug information in separate documents. In cases where only one drug is enrolling, one informed consent may be used in a more traditional fashion.

The ICFs must be written in a language fully understood by the prospective participant, study partner, and caregiver/legally authorized representative (if the participant is cognitively impaired). The investigator or designee shall give the participant adequate opportunity to read the ICF before it is signed and dated. Information will be given in both oral and written form, whenever possible, and in the manner deemed appropriate by the IRB/IEC. Participants must also be given ample opportunity to inquire about details of the study.

If eligibility criteria for an open-label extension period are met, a new written ICF will be obtained from the participant, study partner (if applicable) and/or by the participant's legally authorized representative accordingly.

The opportunity to donate post-mortem brain tissue will be discussed. Interested participants will be provided additional details and a brain donation informed consent will be signed. The DIAN-TU Neuropathology Core (DIAN-TU NPC) will conduct a neuropathologic assessment of each participant recruited to the DIAN-TU who consents to a brain donation and comes to autopsy. Each participating DIAN-TU center will coordinate with the DIAN-TU-NPC to ensure that a brain donation is successful, and that tissue will be preserved (freezing the right half of the brain and fixing the left hemibrain in formalin according to the DIAN-TU NPC manual instructions) and subsequently transported to the DIAN-TU-NPC. To ensure standardized methods and uniform assessment of tissue across DIAN-TU sites, the DIAN-TU sites and NPC will undertake a neuropathologic assessment as described in the *DIAN-TU Brain Donation and Neuropathology Program Manual*.

6.1.2 Family History/Age at Onset Assessment/Demographics/Study Partner Information

Family history, specifics of family mutation and age at onset assessment as well as demographic and study partner information will be collected during the CRI screening visit (CRI Screen) or treatment screening period (V1) and confirmed at the CRI Entry or baseline visit (V2). See the *Global Manual of Operations* for details of the age at onset assessment and the required family/pedigree genetic mutation documentation.

6.1.3 Medical/Treatment History, Concomitant Medications, Adverse Event Assessment

At all visits, the participant's clinically significant medical history and names and dosages of all medications will be reviewed. Medications taken within 90 days of any screening visit (CRI Screen/V1) will be obtained at the respective visit (CRI Screen/V1) and reviewed at all subsequent visits. Prior medications taken for dementia and any interval changes in medications including over-the-counter medications should be reviewed at every visit. Use of alcohol, caffeine, and abused substances will be reviewed. Interval history and presence and severity of any adverse events will be documented at follow-up visits.

6.1.4 Clinical Assessment

The full clinical assessment is performed by interviewing the study partner and participant at CRI Entry, baseline (V2), and annual visits for both the CRI and treatment periods; for certain populations, the MMSE is to be completed at the 26 week (approx. 6-month) visit between annual visits (timing for specific study populations is provided in the CRI appendix and each drug-specific appendix). Audio recordings of some assessments will be made for quality control; see *Global Manual of Operations* for details. The following test instruments will be administered:

a. Clinical Dementia Rating (CDR) and calculation of CDR-SB. CDR-SB includes supplemental boxes for language and behavior.
b. Assessment of clinical diagnosis (Clinician judgment of symptoms)
   ***NOTE**: For each participant, the CDR and assessment of clinical diagnosis should be administered by the same experienced clinician at all visits. Whenever possible, the CDR rater should not be involved in other assessments (e.g., MMSE, FAS, GDS, NPI-Q) or in cognitive testing.*
c. Geriatric Depression Scale (GDS)
d. Functional Assessment Scale (FAS)
e. Neuropsychiatric Inventory Questionnaire (NPI-Q)
f. Mini-Mental State Examination (MMSE)

See the *Global Manual of Operations* for details of administration. All staff administering these batteries must be appropriately trained and certified as specified in the *Global Manual of Operations* for the trial.

6.1.5 Physical and Neurological Examination

Physical examination will include skin, head, eyes, ears, nose and throat, respiratory, cardiovascular, abdomen, lymph nodes and musculoskeletal.

A complete neurological examination will also be completed. At visits after CRI entry and/or baseline, any clinically significant changes will be documented and reported.

6.1.6 Vital Signs

During the CRI period, blood pressure, heart rate, respiratory rate, temperature, and weight will be collected at CRI Screen, CRI Entry, and annual visits. Height will be collected at CRI entry and annual visits only.

During the treatment period, blood pressure, heart rate, respiratory rate and temperature will be collected at all visits. Height will be measured at least at baseline (V2), and weight will be measured approximately every 3 months starting at baseline unless otherwise specified in the drug-specific appendix. Weight collected between on-site annual visits may be obtained at a medical facility where participants receive safety MRIs or at the participants' homes.

6.1.7 Electrocardiogram

A standard 12-lead ECG will be performed at the indicated visits based on the CRI period and study drug arm requirements. Refer to each drug-specific appendix for more details.

For the CRI period and gantenerumab OLE, ECGs will be performed and read locally by a qualified physician or cardiologist, and investigators are to ensure no evidence of exclusionary findings.

For other treatment arms, a central read vendor will be utilized. The site principal investigator or designated sub-investigator will be responsible for initial read on ECGs done at baseline (V2). In the event that the central read becomes available after study drug is administered and is exclusionary when the local read was not, the site principal investigator or designated sub-investigator, in consultation with the PAL, Medical Director or designee, will decide if the participant should continue in the study. A discrepancy between the local and central read will not be considered a protocol deviation. When there are differences in ECG interpretation between the investigator and the cardiologist at the central ECG laboratory, the investigator's interpretation will be used for study entry and immediate participant management.

Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes. ECGs done at visits conducted at sites other than the DIAN-TU site may be done at a sponsor approved local site or by a home health nurse. These will be sent to the central reader and will also be available to the host DIAN-TU site.

6.1.8 C-SSRS

The Columbia Suicide Severity Rating Scale (C-SSRS) will be administered at screening (V1) and baseline (V2), and generally approximately every 3 months thereafter for the first 2 years during the treatment period. The C-SSRS may then be administered less frequently, i.e. approximately every 6 months and/or annually for the remaining duration of the study. Refer to the drug-specific appendices for exact timing.

The C-SSRS will be administered at CRI Entry during the CRI period.

6.1.9 Genetic Testing

Determination of mutation status for DIAD causing variants (*APP*, *PSEN1*, *PSEN2*) and *APOE* genotype will be performed in the trial-designated CLIA-approved laboratory at CRI Screen visit or screening (V1). The results from the CLIA-approved laboratory will be used for purposes of the DIAN-TU-001 study (e.g., for randomization) but will not be communicated to the participants or sites. Participants who wish to learn their DIAD mutation status, or when required for study entry, will be referred for genetic counseling and testing.

Blood samples for provenance[5] testing will be obtained at the CRI Entry visit or baseline visit. Genetic testing results from the CRI period may be used to fulfill the required testing at screening and baseline for the treatment period.

For an open-label extension (OLE) period, if the participant does not know their genetic status and is interested in joining the OLE, the clinical genetic report generated from the study's genetic testing at trial entry may be provided to the appropriate party managing the genetic counseling and disclosure for the participant, i.e., the PI or genetic counselor.

In addition to mutation status, genetic factors that may affect or explain responses to treatments will be explored. Specifically, the genetic profile (both RNA and DNA) of cells found in both CSF and blood samples collected during the trial will be studied. These data will not inform participant care but have the potential to inform researchers of the mechanisms of the study drug on important aspects of Alzheimer's disease biology.

6.1.10 Clinical Laboratory Tests

Clinical laboratory testing includes hematology with differential, chemistry (including liver enzyme tests and electrolytes), and urinalysis (macro and micro). In addition, TSH, vitamin B_{12} levels, hemoglobin A1c, PT, PTT, and INR are obtained only at the CRI Screen and screening visit (V1). Drug-specific appendices may require additional testing; refer to the drug-specific appendices and central laboratory manual for a complete list of analytes to be tested for each drug arm.

Clinical laboratory samples will be obtained and sent to a central laboratory for analysis. During the CRI period, laboratory values obtained at CRI Screen must be reviewed prior to completion of CRI Entry. Laboratory values obtained at screening (V1) must be reviewed prior to completion of baseline (V2) biomarker measures (PET imaging, vMRI, LP-CSF). The site principal investigator or designated sub-investigator must review all laboratory results and document any clinically meaningful abnormal results as an AE; see Section 7.1.1 for criteria to determine if an abnormal result is clinically meaningful. If results from the central laboratory for coagulation studies are unavailable at the baseline visit, results from a local laboratory may be used to confirm that a participant is able to continue with baseline visit procedures, including randomization and study drug dosing. Central lab samples should be sent and used for study reporting purposes. Any clinically meaningful abnormal result that occurs during the study (after screening) should be repeated within an appropriate time frame (as determined by the site principal investigator or designated sub-investigator and/or PAL, Medical Director or designee).

Refer to Section 7 (Safety and Adverse Events) for further details regarding adverse events.

[5] Provenance testing is performed for quality assurance purposes to ensure that genetic blood sample obtained at baseline visit is from the same individual as the sample obtained at the screening visit.

Pregnancy testing – people of childbearing potential only

During the CRI period, serum pregnancy testing will be performed at the CRI Screen visit and urine pregnancy testing will be performed at annual visits for women scheduled for [^{18}F]MK-6240 PET scans. During the treatment period, serum pregnancy testing will be performed at screening (V1) and the safety follow-up visit; and urine pregnancy testing will be performed at all other visits. Pregnancy tests must be confirmed as negative prior to dosing with study drug. Urine pregnancy test must be completed and confirmed as negative either the day of or the day prior to any PET scan. Refer to drug-specific appendices for OLE collection timing.

***NOTE**: Post-menarchal, pre-menopausal people who have undergone tubal ligation are required to have pregnancy testing performed as scheduled at treatment visits. In cases where urine collection proves difficult based on a participant's symptom progression, e.g., incontinence, alternative methods for pregnancy testing may be used with prior sponsor approval.*

6.1.11 Drug-specific Testing

There will be specific laboratory tests for each study compound (e.g., drug levels for pharmacokinetics [PK] and immunological monitoring for immunotherapy including anti-drug antibodies [ADA]). Frequency and specific visit requirements will be specified in each drug-specific appendix. Refer to the central laboratory manual and the *Global Manual of Operations* for additional details on specific sample collection and processing procedures.

6.1.12 Stored Samples (Blood and DNA)

Selected samples (e.g., plasma, DNA, buffy coats, and CSF cell pellets), will be collected and stored for future use so that testing for as yet undiscovered biomarkers can be performed (including, but not limited to, protein biomarker identification, single-gene or genome-wide analyses, epigenetics, single cell RNA). Stored samples may also be used to address regulatory inquiries or for additional monitoring of anti-drug antibodies or other drug-specific analyses. **Because of future trials platform needs, samples will not be discarded or destroyed unless the DIAN-TU determines there is no use for them, or they can no longer be stored.**

Types of samples to be collected, frequency, and specific visit requirements are specified in the drug-specific schedule of visits. Refer to the central laboratory manual for additional details on specific sample collection and processing procedures.

The biomarkers chosen as endpoints for this study were based on currently available data, but new biomarkers are likely to emerge in the coming years. These samples will be used for future studies on the mechanism of action of Alzheimer's treatments and other studies related to neurodegenerative disorders under the supervision of Washington University and the DIAN-TU. These samples will be stored using the participant identification number. Samples will be stored indefinitely unless otherwise specified, and samples will not be discarded or destroyed

unless the DIAN-TU determines there is no use for them or they can no longer be stored. Collection and storage of these samples is mandatory unless prohibited by local laws.

6.1.13 Study Drug Administration

Study drug dosing may be performed at the DIAN-TU site, or for participants who live at a distance from the host DIAN-TU site, dosing may be administered by the trial-designated home health nurses or at other trial-identified locations. Study staff who administer study drugs will have training and supplies necessary to treat allergic reactions including anaphylaxis.

Details of study drug administration or dispensing should be recorded; see *Global Manual of Operations* for details.

Requirements for monitoring participants after study drug administration are detailed in each drug-specific appendix.

For the study drug administration visits following the occurrence of a safety MRI, the site principal investigator or designated sub-investigator must review the MRI central read prior to proceeding with the subsequent dose administration for parenterally administered treatments.

6.1.14 Cognitive Testing

Cognitive batteries administered in the gantenerumab and solanezumab double-blind treatment arms can be found in previous protocol versions. Cognitive testing should be performed early in the day before other invasive or stressful procedures.

6.1.14.1 Gantenerumab OLE Period

The Complete Cognitive Battery will be performed annually at the DIAN-TU site, and a subset of the testing battery (the Cognitive Battery Subset) will be performed approximately every 6 months. See the *Gantenerumab OLE DIAN Trials Unit Cognition Core Procedures Manuals* for additional details and suggested timing for administration of cognitive testing.

All staff administering these batteries must be appropriately trained and certified as specified in the *Gantenerumab OLE DIAN Trials Unit Cognition Core Procedures Manuals*. The following tests will not be administered at any visit to participants who had a CDR of 1 at gantenerumab or solanezumab double-blind baseline (V2) visit: Groton Maze Learning Test, Behavioral Pattern Separation Object Task, and MAC-Q.

Complete Cognitive Battery (annual visits)

Cognitive measures to be obtained at the OLE baseline visit (OLE V1) and annual OLE visits are administered at a DIAN-TU site and include the iPad-administered and conventional cognitive (pen/paper) tests listed below.

iPad-administered Cognitive Testing:

- International Shopping List Test (12-Item Word List Learning): 3 learning trials, Immediate Recall, 30-min Delayed Recall (Cogstate)
- Groton Maze Learning Test*: Timed Chase Task, 5 learning Trials, Immediate Recall, 30-min Delayed/Reversed Recall (Cogstate)
- Cogstate Detection Task
- Cogstate Identification Task
- Cogstate One Card Learning Test
- Cogstate One-Back Task
- Behavioral Pattern Separation Object Task*
- MAC-Q*

Conventional Cognitive Testing (Pen/Paper):

- Trailmaking Test parts A & B
- WMS-R Digit Spatial Span Forward and Backward
- WAIS-R Digit-Symbol Substitution Test
- Raven's Progressive Matrices (Set A)
- Category Fluency (Animals & Vegetables)
- WMS-R Logical Memory/Paragraph Memory (Immediate & Delayed Recall)

*These tests should not be administered at any visit to participants who had a CDR of 1 at their original double-blind period baseline (V2) visit.

Cognitive Battery Subset (every six [6] months when not annual):

The subset of the complete cognitive battery will be administered by the site or trial-certified cognitive rater at the gantenerumab OLE visits occurring at the approximate 6-month treatment visits between annual visits and includes the iPad-administered and conventional cognitive (pen/paper) tests listed below.

Conventional Cognitive Testing (Pen/Paper):

- Trailmaking Test parts A & B
- WMS-R Digit Span
- WAIS-R Digit-Symbol Substitution Test
- WMS-R Logical Memory (Immediate & Delayed Recall)

In addition, the cognitive measures listed below will be administered by the site or trial-certified cognitive rater:

iPad-administered Cognitive Testing

- International Shopping List Test (12-ltem Word List Learning): 3 learning trials, Immediate Recall, 30-min Delayed Recall (Cogstate)
- Groton Maze Learning Test: Timed Chase Task, 5 learning Trials, Immediate Recall, 30-min Delayed/Reversed Recall (Cogstate)*

- Cogstate Detection Task
- Cogstate Identification Task
- Cogstate One Card Learning Test
- Cogstate One-Back Task

*These tests should not be administered at any visit to participants who had a CDR of 1 at their original double-blind period baseline (V2) visit.

6.1.14.2 Cognitive Run-In Period and Tau Drug Arms: DIAN-TU Harmonized Cognitive Battery

The DIAN-TU Harmonized Cognitive Battery will be performed approximately every 26 weeks (~6 months) for the CRI secondary prevention population and for tau drug arms; and every 52 weeks (annually) for the CRI primary prevention population by a trial-certified cognitive rater at either the host DIAN-TU site or home health nursing visit.

Cognitive measures to be obtained in the Cognitive Run-In (CRI) and tau-targeted study drug arms include the below listed tests.

DIAN-TU Harmonized Cognitive Battery:

- Memory Complaint Questionnaire (MAC-Q)
- Buschke and Grober Free and Cued Selective Reminding Test-Immediate Recall (FCSRT-IR)
- WMS-R Logical Memory/Paragraph Memory (Immediate & Delayed Recall), Alternate Paragraph for Logical Memory I & II – Version A (Immediate and Delayed) and Alternate Paragraph for Logical Memory I & II – Version B (Immediate and Delayed)
- Category Fluency (Animals)
- WAIS-R Digit-Symbol Substitution Test
- Trailmaking Test Parts A & B
- WMS-R Digit Spatial Span Forward and Backward

IMPORTANT for baseline treatment visit 2 (V2): If the CRI period is open to enrollment, a CRI period may last until a study drug arm opens for randomization, but no longer than approximately 3 years. If a participant is taking part in a CRI period, a minimum of 8 weeks must elapse between the participant's last administration of a cognitive battery during the CRI period and administration of the baseline (V2) cognitive battery.

Smartphone-based Cognitive Assessments

Smartphone-based cognitive (Ambulatory Research in Cognition [ARC]) assessments will be administered to participants using a mobile phone application, developed at Washington University in St. Louis. These tests will include measures of episodic memory, attentional control, and processing speed and are administered multiple times per day over the course of several days. These assessments will be self-administered by the participants on their personal

smartphones. If participants do not own a smartphone or their device does not meet minimum specifications, a study phone will be provided.

Compliance with the smartphone-based cognitive measures is considered exploratory and non-participation will not be considered reason for discontinuation in the study and will not be considered protocol deviations. Based on operational and regulatory considerations, the study sponsor will determine which sites will administer the smartphone-based cognitive assessments, with the explicit goal of full site participation.

Participants will be instructed on installation and setup of the ARC application at their CRI screening visit (CRI Screen) or drug arm screening visit (V1). Participants will complete the first week of assessments immediately following the CRI screening visit or screening visit (V1) of a treatment arm. Participants will continue to complete assessments approximately every 26 weeks (approximately 6 months) for the secondary prevention population and every 52 weeks (annually) for the primary prevention population after the CRI entry visit (CRI Entry) and/or baseline (V2) of a treatment arm.

6.1.15 Baseline and Annual Magnetic Resonance Imaging (MRI)

For all drug arms, MRIs performed at the DIAN-TU site at annual visits starting with CRI Entry and/or baseline [V2] visits, will include structural and functional MRI and other additional MRI endpoints in addition to sequences for safety monitoring. All MRIs, including safety MRI scans performed off site, if applicable (see Section 6.1.16), will utilize standardized sequences that include fluid-attenuation inversion recovery (FLAIR) and T2*-weighted gradient-recalled-echo (GRE) sequences. Additional scheduled safety MRI assessments between annual visits may be scheduled based on study drug arm (see each drug-specific appendix).

MRIs use a standardized protocol specified by the DIAN-TU Imaging Core (see *MRI Technical Manual* for specific sequences*)*. The DIAN-SHORT protocol, a core set of MR sequences necessary for safety MR and PET processing, will be used for off-site MRIs and may be used at the host site for those whom, in the estimation of the site principal investigator, would not be able to complete the full-length protocol (e.g., participants who are unable to remain still for the full MR session, approximately 45 minutes in duration). MRI should be performed before lumbar puncture (if on the same day) or scheduled to be on a different day than the lumbar puncture.

Scanners will be evaluated and qualified by the Mayo-ADIR Clinic prior to participant scanning, and ongoing quality control of the MRI scans will be performed at the Mayo-ADIR Clinic.

MRIs will be uploaded to the trial-designated imaging data management system (DIAN Central Archive [DCA]).

Images should be uploaded within 24 to 48 hours of scan completion; failure to upload the images within 3 working days of receipt of the images will be considered a protocol deviation. **Images from the CRI Entry, CRI annual visits, baseline MRI (V2), and all annual visit MRIs should be uploaded immediately** after these scans are completed as the findings of these MRIs

can impact inclusion in the study (CRI Entry and baseline [V2] MRI) and thereafter alter dispensing/administration of next dose(s) of study drug.

Volumetric analysis of the baseline and the annual MRIs will be performed by Washington University and will include measures of hippocampal volume, ventricular volume and whole brain volume. Site investigators will not receive results of the volumetric analysis. All MRI scans will be analyzed for amyloid-related imaging abnormalities (ARIA) and for incidental findings at the Mayo-ADIR Clinic; this includes safety MRIs (see Section 6.1.16). Findings on the baseline MRI will determine eligibility; therefore, results of the baseline read will be made available before randomization and first dispensing/administering of study drug. ARIA findings during the study may result in a change or halting of study drug dosing; see each drug-specific appendix for additional information. See *Global Manual of Operations* for additional details and *MRI Technical Manual* for technical information.

Additional MRI examinations for the OLE period will be listed in the drug-specific appendices.

6.1.16 Safety Magnetic Resonance Imaging (MRI)

Safety MRIs on 3T scanners will be done primarily to monitor for ARIA. Safety MRIs may be done at the host DIAN-TU site or, for participants who live at a distance from the host DIAN-TU site, at a site closer to the participant's home in order to reduce participant travel burden. When not performed at the DIAN-TU site, safety MRIs may be performed at an ADNI/ADCS site if possible or at a 3T scanner near the participant's home. Local centers not previously qualified as a DIAN, ADCS or ADNI-equivalent site will be pre-qualified for the DIAN-TU trial protocol by the Mayo-ADIR Clinic. With the exception of the MRIs done at the DIAN-TU site during annual visits, safety MRIs should be performed on the same scanner throughout the trial.

Standardized sequences will be used for these scans and will include fluid-attenuation inversion recovery (FLAIR) and T2*-weighted gradient-recalled-echo (GRE) sequences. See *MRI Technical Manual* for additional information. Sites must ensure that study visits are scheduled so that MRI images are uploaded and available for central read at least 3 to 5 working days before next administration of study drug for parenterally administered drugs.

A central read for safety purposes (e.g., analysis of ARIA) will be completed at the Mayo-ADIR Clinic within 1 week (5 working days) of upload for routine exams; and within 24 hours for the MRIs done for all drug arms at CRI Entry, and treatment period baseline (V2), and annual visits preceding dose administration.

A central read for safety purposes may also be completed for annual OLE visits and routine exams as specified in the drug-specific appendices.

The central read results will be communicated to site principal investigators (site PIs) or designated sub-investigator, Project Arm Leader (PAL), and Medical Director or designee. This communication will occur at least one week before the next scheduled drug dispensing/administration. Extent of ARIA-E and presence of definite and possible ARIA-H changes will be reported; reports including significant or new definite findings will be flagged

for review by site principal investigator or designated sub-investigator, PAL, and sponsor Medical Director or designee. The site principal investigator or designated sub-investigator will review the findings and drug-specific guidelines for dosing adjustment (see each drug-specific appendix) with the PAL. The PAL will confer with the Medical Director or designee who has final authority on dose adjustment decisions (e.g., extra study visit, repeat or more frequent safety MRIs, suspension of study drug administration or dose adjustment; see each drug-specific appendix for discussion of ARIA-related interventions). The Medical Director has the final decision on whether a dose is released for treatment. See *Global Manual of Operations* for further details on communication between the site principal investigator or designated sub-investigator, PAL, and Medical Director or designee. See *MRI Technical Manual* for technical information.

When an imaging visit precedes a visit where study drug is parenterally administered, it is the responsibility of the DIAN-TU site principal investigator or designated sub-investigator to review the central read safety MRI results before study drug administration and communicate any changes in study drug administration to the site staff or home health nurse preparing and administering the study drug.

Local read for safety MRIs is not required for purposes of this study but should be performed if needed in accordance with local requirements. Should a local read be obtained and be different from the central read, central read has priority for study purposes.

6.1.17 Lumbar Puncture (LP) – Cerebrospinal Fluid (CSF)

Cerebrospinal fluid (CSF) analysis for biomarkers will be performed at baseline (V2) and subsequent time points as outlined in the drug-specific appendices. Lumbar puncture (LP) is to be performed at the DIAN-TU site to collect 25 mL of CSF while the gantenerumab open-label extension arm will continue to collect at least 15 to 20 mL of CSF.

A sample of CSF will be sent to a local lab for cell counts and differential as well as glucose and protein measurement (estimated at approximately 2 mL); each site should confirm with their local lab the volume of CSF needed for these studies. Because CSF biomarkers are the biomarker endpoint for some of the study drug arms, at least 23 mL CSF should be sent for biomarker analysis (15 mL CSF for gantenerumab OLE); this is in addition to the CSF obtained for the local lab studies. Cell pellets will be obtained from the 23 mL of CSF collected for biomarker analysis for genetic analysis and mechanistic studies of drug actions; cell pellets will not be collected for participants in the gantenerumab OLE arm. It is essential that at least 23 mL of CSF is collected at baseline of any blinded study periods before any dosing occurs. If less than 23 mL is collected for biomarker analysis at the baseline visit, contact the sponsor prior to dispensing/administration of study drug to determine if participant is eligible to remain in the trial. See central laboratory manual and the *Global Manual of Operations* for additional details regarding required LP and collection procedures and materials, processing instructions, and shipping of CSF samples**.**

The LP should be performed in the morning, at approximately 8 AM local time, **under fasting conditions** (water is allowed and encouraged). LPs should be conducted as close to the baseline collection time as possible at each subsequent visit. CSF should be collected using the traditional gravity drip method. Sites should obtain approval from the sponsor, before LP is performed, for the use of alternative methods or needles (e.g., aspiration if using a very small gauge needle, use of a needle type/size other than the sponsor-mandated needle outlined in the *Global Manual of Operations* and provided to the sites for use). If LP proves technically difficult, early referral for LP under fluoroscopy is expected.

6.1.18 Positron Emission Tomography

For the CRI period, positron emission tomography (PET) with the [^{18}F]MK-6240 tracer will be performed for participants that are within −10 to +10 (inclusive) of EYO (secondary prevention) at CRI Entry and annual CRI visits as specified in the appendix. Tau PET is not completed for participants in the primary prevention population (−25 to −11 EYO).

For all study drug arms, PET imaging with selected tracers will be performed at baseline (V2), at the week 52 (V15), 104 (V28), and 208 (V54) visits of double-blind periods; additional imaging time points may be required as specified in each drug-specific appendix.

In OLE periods, PET imaging with selected tracers will be performed per drug-specific appendices.

The type of PET imaging is drug-specific (see each drug-specific appendix) and may include one or more of the following:

Pittsburgh Compound B ([^{11}C]PiB-PET) PET Imaging – *Excluding CRI Period*

[^{11}C]PiB-PET imaging will be performed at DIAN-TU qualified sites at baseline (V2) and at the weeks 52 (V15), 104 (V28), and 208 (V54) visits of the double-blind period, at minimum, and at baseline and annually during OLE. Additional time points may be required as specified in each drug-specific appendix.

[^{11}C]PiB-PET imaging may be performed at other trial-qualified sites if the host DIAN-TU site is unable to perform PET imaging. For each participant, the same scanner should be used for all [^{11}C]PiB-PET imaging sessions. See *PET Technical Procedures Manual* for additional details. [^{11}C]PiB-PET manufacturing and imaging protocols will be standardized across all participating sites. A DIAN-TU radiochemistry review team will audit and qualify [^{11}C]PiB manufacturing and conduct ongoing QC of PiB batch records. The University of Michigan will provide quality control on [^{11}C]PiB-PET images. Images will be uploaded to the imaging data management system, DCA. Image processing and analyses will be performed by Washington University.

For people of childbearing potential (POCBP), a urine pregnancy test must be completed and confirmed as negative before the first PET scan. If PET scans are spread over more than one day, a urine pregnancy test should be completed either the day of or day prior to any PET scan.

Scan Acquisition: Participant preparation consists of intravenous catheterization followed by the bolus injection (over 10 to 60 sec) of [^{11}C]PiB at dosage: 8 to 18 mCi. There are two acceptable procedures for obtaining the [^{11}C]PiB-PET scans. In one approach, a 30-minute scan will be started 40 minutes post-[^{11}C]PiB-PET injection. The other approach involves a 70-minute dynamic scan that is started at the time of PiB injection. Further details of the PiB-PET scan acquisition are outlined in the *PET Technical Procedures Manual*.

Participants should be scanned on the same scanner as was utilized at the baseline visit, unless the participant changes DIAN-TU sites. In the event an issue arises where a scanner becomes unavailable, a site may get sponsor approval to be scanned on another DIAN-TU approved scanner if there is one available to them and it is allowable per IRB/IEC guidelines.

Fluorodeoxyglucose PET (FDG-PET) – *Excluding CRI Period*

For treatment arms, uptake of 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG-PET) will be performed for participants enrolled in selected study drug arms at baseline (V2) and at minimum, the week 52 (V15), 104 (V28), and 208 (V54) visits of double-blind periods, and annually during OLE, or as described in the schedule of visits in each drug-specific appendix.

FDG-PET will be done at DIAN-TU qualified sites using DIAN-TU protocol as specified in the *PET Technical Procedures Manual*. FDG-PET imaging may be performed at other trial-qualified sites. For each participant, the same scanner should be used for all FDG-PET imaging sessions. Participants should be fasting for 4 hours before the FDG-PET is performed. The University of Michigan will provide quality control on FDG-PET images. Images will be uploaded to the imaging data management system, DCA. Image analyses will be performed by Washington University.

For POCBP, a urine pregnancy test must be completed and confirmed as negative before any PET scan. If PET scans are spread over more than one day, a urine pregnancy test should be completed either the day of or day prior to any PET scan.

Scan Acquisition: Typically, the PiB-PET scans will precede the FDG scans on the same day; however, this arrangement is for convenience to the participant and coordinators but is not a requirement (see *Global Manual of Operations* for schema). After completion of PiB-PET scanning, participants will be moved to a dimly lit, quiet room and **5 mCi** of FDG will be injected as a bolus. Doses administered that are within 10% of the protocol-required dose per standard clinical practice will not be considered a protocol deviation. About 20 minutes later, participants will be repositioned in the PET scanner, and FDG PET scans will be acquired in dynamic, 3D mode beginning 30 min (± 30 seconds) after injection of FDG for 30 min (consisting of 6 x 5 min frames). Details of the PET scan acquisitions are outlined in the *PET Technical Procedures Manual*.

Tau PET Imaging

The DIAN-TU-001 trial provides a critical opportunity to investigate the potential for tau imaging to enhance basic understanding of the evolution of tau pathology during the

Alzheimer's disease process, to understand the relationship between tau imaging and tau measurements in CSF and may support a role for tau imaging as a new surrogate biomarker.

For the CRI period, positron emission tomography (PET) with the [^{18}F]MK 6240 tracer will be performed at CRI Entry, week 52 (CRI 5) and week 104 (CRI 9) visits for participants in the secondary prevention population (−10 to +10 EYO).

For the double-blind period of the study drug arms, tau scans will be performed at DIAN-TU qualified sites at minimum, at baseline (V2), and week 52 (V15), 104 (V28), and 208 (V54) visits; and may be performed annually in open label periods. Refer to the below individual tracer details and drug-specific appendices for the individual tracer to be used and schedule to be followed.

Based on the currently available data for tau PET in the DIAN-OBS study, it is highly unlikely that participants considered for primary prevention will have evidence of tau PET abnormalities. Therefore, those qualifying for CRI period who are younger than −10 years from estimated age at symptom onset (−25 to −11 EYO; primary prevention population) will not undergo tau PET.

[^{18}F]*AV-1451 PET – Gantenerumab OLE Only*

The gantenerumab and solanezumab double-blind treatment arms utilized the [^{18}F]AV-1451 tracer (Avid Radiopharmaceuticals, Inc.) via protocol addendum for the double-blind period rather than as part of the main study protocol due to tracer access constraints. For consistency, the gantenerumab OLE period will continue to collect [^{18}F]AV-1451 tau PET annually however, it will be included in the drug-specific appendix.

Avid Radiopharmaceuticals, Inc., or a DIAN-TU radiochemistry review team, will audit and qualify [^{18}F]AV-1451 manufacturing and conduct ongoing QC of [^{18}F]AV-1451 batch records. The University of Michigan will provide quality control on [^{18}F]AV-1451 images. Images will be uploaded to the imaging data management system, DCA. Image analyses will be performed by Washington University. Specific imaging acquisition protocols designed to ensure consistency across sites will be provided in a technical manual. The scanning technologist will be blinded to the participant's treatment assignment (e.g., whether participant is on active or placebo treatment in the DIAN-TU-001 study).

POCBP are to have a confirmed negative pregnancy test (HCG) on the day of [^{18}F]AV-1451 PET imaging session, before [^{18}F]AV-1451 dose administration. If PET scans are spread over more than one day, a pregnancy test should be completed either the day of or one day prior to any PET scan.

Scan Acquisition: See *PET Technical Procedures Manual* for additional details. PET/CT is the preferred imaging modality for [^{18}F]AV-1451 imaging. In the event an issue arises where a scanner becomes unavailable, a site may get sponsor approval to be scanned on another DIAN-TU approved scanner if there is one available to them and it is allowable per IRB/IEC guidelines.

There are two acceptable procedures for obtaining the [^{18}F]AV-1451 PET scans:

1. The preferred option will be for participants to receive a single IV bolus injection of approximately (240 MBq) **6.5 mCi** of [^{18}F]AV-1451 injection followed by a saline flush. Scanning will start at the same time as the injection and continue for a total of 105 minutes. If needed, the participant may take up to a 15-minute break after the first 60 minutes of scanning, and scanning should resume immediately after the break.
2. For participants that are not able to tolerate or who do not wish to undergo the full-length scan, a continuous 30-minute brain scan (6 acquisitions of 5-minute duration) should be performed with scanning to start approximately 75 minutes following injection.
3. DOSE PREPARATION: To allow for a convenient injection volume of greater than 1 mL, [^{18}F]AV-1451 may be diluted aseptically with sodium chloride 9 mg/mL (0.9%) solution for injection to a maximum dilution of 1:5 by the end-user. Diluted product should be used within 3 hours of dilution.

The injection site will be observed for evidence of inflammation or damage to the surrounding tissue where the dose was injected, and the participant will be requested to void after completion of the PET scans. Participants will be observed continuously for signs of adverse events (AE) or serious adverse events (SAE).

Information on the tau PET tracer and additional details regarding tau PET scanning, including pre- and post-imaging procedures, will be included in the *PET Technical Procedures Manual*.

[^{18}F]*MK-6240 PET - Cognitive Run-In Period and Tau Drug Arms*

The CRI period and tau drug arms will utilize [^{18}F]MK-6240 tau PET tracer, if/as specified in the drug-specific appendices. [^{18}F]MK-6240 may be optional for some global sites based on its availability at the discretion of the sponsor and will be limited to the secondary prevention population (i.e., participants within −10 to +10 years (inclusive) of the predicted or actual age at cognitive symptom onset). [^{18}F]MK-6240 PET will be done at qualified DIAN-TU sites using DIAN-TU protocol as specified in the *PET Technical Procedures Manual*. [^{18}F]MK-6240 PET imaging may be performed at other trial-qualified sites to ensure participants at sites with no, or limited, access to the tracer can still complete the scan.

[^{18}F]MK-6240 will be produced by a study-approved manufacturing cyclotron facility. Images will be uploaded to the imaging data management system, DIAN Central Archive (DCA). Image analyses will be performed by Washington University. Specific imaging acquisition protocols designed to ensure consistency across sites will be provided in a technical manual. The scanning technologist will be blinded to the participant's treatment assignment (e.g., whether participant is on active or placebo treatment in the DIAN-TU-001 study).

POCBP are to have a confirmed negative urine pregnancy test (HCG) on the day of [^{18}F]MK-6240 PET imaging session, before [^{18}F]MK-6240 dose administration. If PET scans are spread over more than one day, a urine pregnancy test should be completed either the day of or one day prior to any PET scan.

[^{18}F]MK-6240 administration: Participants will receive a single intravenous bolus injection of 185 MBq (5 mCi). The injected activity will not be less than 159.1 MBq (4.3 mCi) and no more than 222 MBq (6 mCi). The total injected volume will not be more than 10 mL followed by a 10 mL normal saline (0.9% NaCl) flush.

The injection site will be observed for evidence of inflammation or damage to the surrounding tissue where the dose was injected. Participants will be observed continuously for signs of adverse events (AE) or serious adverse events (SAE).

Scan Acquisition: See *PET Technical Procedures Manual* for additional details. PET/CT is the preferred imaging modality for [^{18}F]MK-6240 imaging. In the event an issue arises where a scanner becomes unavailable, a site may get sponsor approval to be scanned on another DIAN-TU approved scanner if there is one available to them and it is allowable per IRB/IEC guidelines.

Participants will receive the [^{18}F]MK-6240 injection and rest quietly in an uptake room. At exactly 80 minutes following the injection, participants will undergo a continuous 30-minute brain scan consisting of 6 x 300 sec frames.

Standard Brain Attenuation Scan for attenuation correction:

- PET/CT scanner: Acquire a low dose CTAC scan with topogram just prior to the emission data acquisition scan for [^{18}F]MK-6240.
- PET only scanner: Acquire a transmission scan using rod source for 5 to 10 minutes just prior to the emission data acquisition scan for [^{18}F]MK-6240.
- A *second* CT or transmission scan must be acquired if the participant is removed from the scanner and resumes scanning after a break.

Information on the tau PET tracer and additional details regarding tau PET scanning, including pre- and post-imaging procedures, will be included in the *PET Technical Procedures Manual*.

6.1.19 Brain Donation Program

The brain donation program allows the entire brain to be forwarded to the DIAN-TU Neuropathology Core (NPC); site-specific arrangements will be made to maximize tissues donated from international sites that have legal restrictions on unconditional whole brain donation. The DIAN-TU NPC will perform a standardized comprehensive neuropathological assessment, implementing the same protocol that is utilized for brain specimens evaluated in the DIAN Observational (DIAN-OBS) study, and coordinate with DIAN-TU Imaging Core to perform post-mortem magnetic resonance imaging of the fixed hemibrain. This approach will facilitate direct comparisons of DIAN-TU cases to the DIAN-OBS cases, which represent the "natural spectrum" of DIAD pathology.

Neuropathological findings in DIAN-TU cases will be evaluated for associations with clinical, genetic, neuropsychological, and neuroimaging data obtained from DIAN-TU investigative sites. Special handling or blinding of the resulting data may be required if the study arm that the

participant was enrolled in is actively ongoing; this is necessary to protect the integrity of the DIAN-TU trial data and alleviate any possibility of compromise.

All operational and logistical details regarding the brain donation program are located within the ***DIAN-TU Brain Donation and Neuropathology Program Manual***.

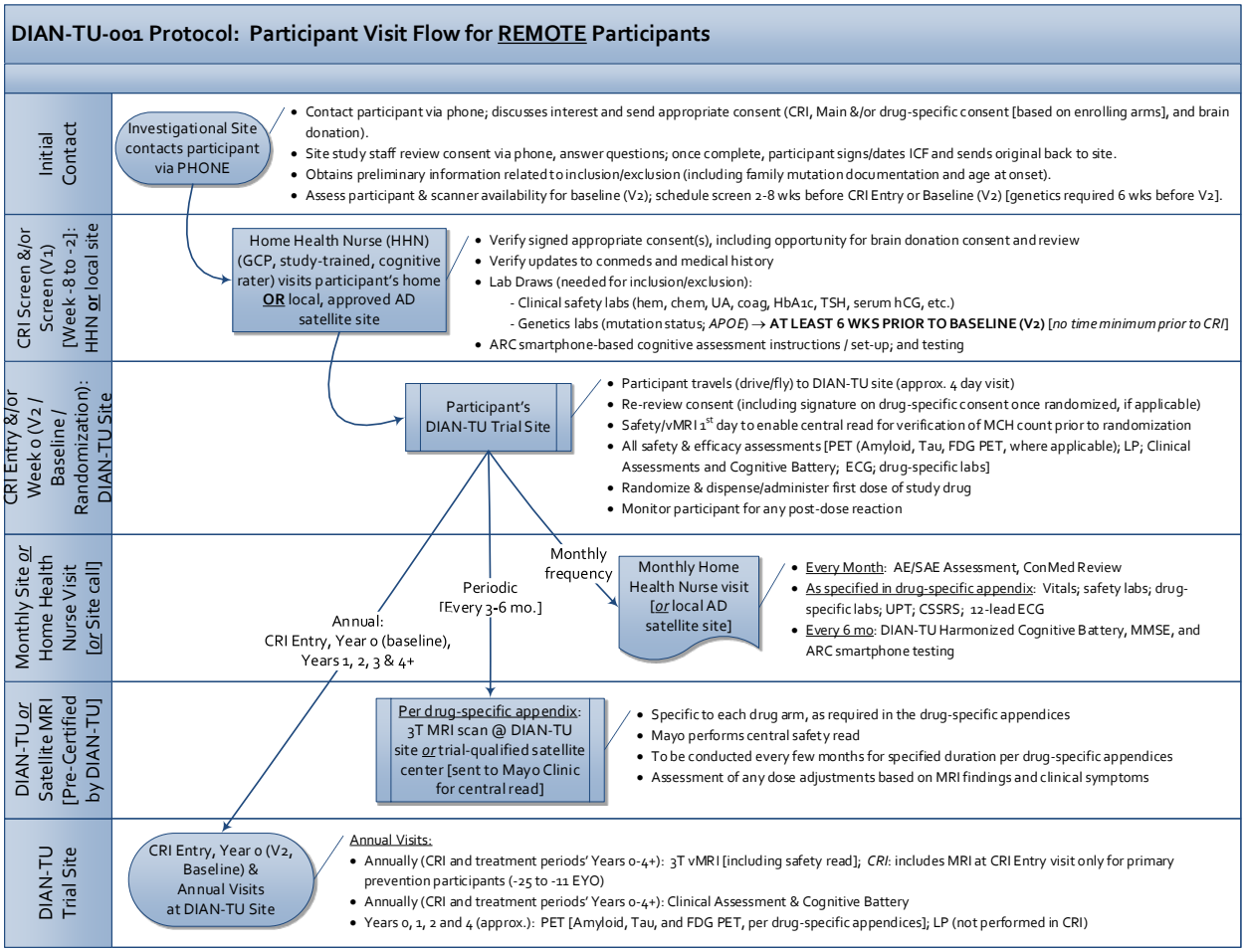
Eligibility: Participants from any DIAN-TU study, or DIAD individuals participating in external studies evaluating the same drugs as in the DIAN-TU platform, are eligible to participate in the DIAN-TU Brain Donation Program.

6.2 Overview of Visit Flow

A participant enrolled in a CRI period can transition from the CRI to an open study drug arm at any time, as long as there is a minimum of 8 weeks between the participant's last administration of a complete cognitive battery or subset, or the DIAN-TU Harmonized Cognitive Battery during the CRI period and administration of the baseline (V2) complete cognitive battery. As long as at least 8 weeks have elapsed, the participant can complete their baseline (V2) assessments, including the DIAN-TU Harmonized Cognitive Battery, and continue with the regular drug-specific schedule of events. This 8-week lapse is intended to mitigate carryover effects from repeated testing while also ensuring that participants can be randomized without any significant delays.

Figure 4 provides a general visual representation of the DIAN-TU-001 study visit flow. Note that the figure does not contain all assessments to be performed during the study but is intended to present an overview of the study chronology. Figure 4 shows the visit flow for participants who live at a distance from a DIAN-TU site and have many study visits performed at home. These visits can be performed at the host DIAN-TU site for participants who live nearby or, for participants who live at a distance from the host DIAN-TU site, in the participant's home or another trial-identified location more convenient for the participant. Visits performed in the home or other sites will be performed by a GCP trained home health nurse who has been trained in DIAN-TU procedures.

Figure 4 Overview of Participant Visit Flow



6.3 Study Visits

The schedule of visits for the CRI period is provided in Appendix 1 and for the secondary prevention treatment period screening and baseline visits, Appendix 2. The schedule of visits, including drug-specific tests and frequency of safety MRIs, for each drug arm is provided in each drug-specific appendix. All information on timing of visits refers to calendar days. The sequence and timing of visit procedures is very important. Detailed requirements and suggested timing of events are detailed in the *Global Manual of Operations*. The specific date of the cognitive testing administered during the CRI Entry visit should be used to determine timing of subsequent visits during the CRI period. The specific date during the baseline visit when the first dose of study drug is administered should be used to determine timing of subsequent visits during the treatment period and for calculating time between the screening and baseline visits.

6.3.1 Cognitive Run-in Period

If no study drug arm is available for immediate enrollment or if a future drug arm is stopped prior to the planned completion (e.g., at biomarker interim, drug toxicity), participants may enter into a CRI period which will consist of screening, entry, and follow-up visits. See Appendix 1, Cognitive Run-in Period, for the specific assessments that are required at each visit.

Once a drug arm is open, participants will have a screening visit (V1) conducted either in their home by a home health nurse, or at the DIAN-TU site, to collect safety labs and to reassess the suitability of the participant for entry into the trial (Section 6.3.2).

6.3.2 General Platform Procedures for Screening (Visit 1) in Double-Blind Treatment Periods

The screening period that immediately precedes enrollment into a study drug arm may last up to 8 weeks, starting at the collection of the first screening procedure (e.g., clinical laboratory, cognitive testing).

***Note**: The schedule of visits for screening (V1) and baseline (V2) identify procedures that do not need to be repeated if collected during the CRI period, e.g., genetic testing, family history, demographic and study partner information, medical and treatment history and assignment of study-specific participant identification number.*

Location: Visit 1 procedures may be accomplished at the DIAN-TU site or at the participant's home or other trial-identified location with the trial-designated home health nurse. This visit also includes telephone calls with the DIAN-TU site staff. The participant may be contacted by their host DIAN-TU site by telephone or during a regular DIAN Observational study visit. The participant is given the opportunity to review the informed consent form(s), ask questions and obtain answers, and sign the main ICF (if multiple drug arms are enrolling) or the stand-alone ICF.

Time/Timing: Informed consent must be obtained before any other study procedures. Informed consent, family history, demographic information and medical and treatment history may be obtained before the 8-week screening period begins. Informed consent should be obtained from both participant and study partner. Unless otherwise specified, all other Visit 1 procedures may occur throughout the screening period (2 to 8 weeks before baseline [V2]). **IMPORTANT:** Results from screening clinical laboratory tests and genetic testing must be available before baseline (V2); blood collection for genetic testing must be completed **at least 6 weeks before V2** to ensure genetic results are available for baseline randomization. Genetic testing results from the CRI period may be used. The screening visit in the home ensures participant eligibility before travel (if applicable) to the DIAN-TU site for baseline testing and randomization.

Procedures (all can be performed by DIAN-TU site staff or trial-designated and trained home health nurse or other staff except as noted-see *Global Manual of Operations* and *The arm-specific DIAN Trials Unit Cognition Core Procedures Manuals* for additional details on order and timing of procedures):

- Obtain informed consent (DIAN-TU site staff should be available to answer questions)
- Obtain or confirm family history and determine parental estimated age at onset or participant's actual age at onset (DIAN-TU site staff), if not collected during a CRI period. Estimated age at onset should be determined as outlined in the *Global Manual of Operations*.
- Verify documentation of participant's trial eligible mutation status OR, when allowable per drug-specific appendix, confirm via family pedigree and mutation documentation (proband) that the participant is at 50% risk for a trial-eligible mutation, if not collected during a CRI period
- Collect demographic information and study partner information, if not collected during a CRI period
- Obtain medical and treatment history, including assessment/recording of pre-existing conditions or adverse events; results from CRI period may be used unless the participant or study partner becomes aware of new information.
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature). Weight is not required at this visit, but the participant's self-reported weight may be noted if required for laboratory tests.
- Blood collection:
  - genetic testing (***NOTE****: genetic testing blood sample must be obtained at least 6 weeks prior to Visit 2 to ensure availability for baseline randomization; results from the CRI period may be used.*)
  - clinical laboratory tests, including TSH, vitamin B_{12}, hemoglobin A1c, PT, PTT, and INR
  - serum pregnancy test for POCBP
  - drug-specific analytes (refer to drug-specific appendices)
- Urine collection for urinalysis
- Administration of C-SSRS
- ARC smartphone-based cognitive assessment:
  - Set-up and training
  - Participants will be prompted to begin the testing and will continue to complete the test over a continuous 7-day period.

A study-specific participant identification number is assigned to the participant by the interactive web response system (IWRS). Visit 2 is not scheduled to occur until the results of the clinical laboratory tests are available and the results of genetic testing are entered in IWRS. Genetic testing results from CRI period may be used. Results of genotyping of *APOE* and DIAD-associated genes (*APP*, *PSEN1*, and *PSEN2*) are not sent to the site to ensure genetic blinding is maintained during double-blind treatment periods, when applicable, however may be provided for OLE qualification as specified in Section 6.1.9.

6.3.3 General Platform Procedures for Baseline (Visit 2/First Dose) in Double-Blind Treatment Periods

Location: DIAN-TU site including DIAN-TU qualified imaging centers.

Time/Timing: Approximately a 3- to 4-day visit that is scheduled 2 to 8 weeks after the screening visit and at least **6 weeks after the genetic sample collection**, if genetic testing was not completed during a CRI period. This visit can only take place after results from safety screening labs are documented as consistent with inclusion/exclusion criteria before Visit 2 occurs. Genotyping results will need to be confirmed as received and having completed analysis, but no results will be provided or reviewed by site staff. The study partner participates in some of the procedures at Visit 2 and other annual visits at the DIAN-TU site. If possible, the study partner should accompany the participant to the DIAN-TU site for these visits. If this is not possible, the study partner procedures can be completed via telephone. The sequence and timing of visit procedures is very important. Detailed requirements and suggested timing of events at Visit 2 and at subsequent annual visits are detailed in the *Global Manual of Operations*. Baseline visit procedures may be scheduled over a longer time period of up to 2 weeks for participants who live near the study site or in the event that some study procedures (e.g., PET imaging) are done at a different DIAN-TU site or approved imaging location.

***Notes**: Although participating in the DIAN-TU study may not require that participants know whether they have a mutation associated with dominantly inherited Alzheimer's disease, it will be recommended that all participants undergo genetic counseling prior to starting assigned study drug. Participants in the study might guess (correctly or incorrectly) whether they are on active drug because specific side-effects may occur more often with the active drug compared to the placebo therapy, therefore disclosing mutation status.*

The date during Visit 2 when the first dose of study drug is dosed/administered should be used for determining the timing of all subsequent visits.

Procedures:

- In-person review of informed consent for participants who provided consent over the telephone
- Medical/treatment history, including:
  - Concomitant medications
  - Assessment /recording of pre-existing conditions or adverse events
- Urine pregnancy testing for POCBP
- Blood collection for the following:
  - provenance[6] testing of Screening genetic sample [to confirm specimen identity]; results from a CRI period may be used
  - clinical laboratory tests (hematology, chemistry, urinalysis)

[6] Provenance testing is performed for quality assurance purposes to ensure that blood sample obtained at baseline visit is from same individual as sample obtained at screening visit.

  - stored plasma and/or serum and/or DNA
  - baseline drug-specific tests (as outlined in the drug-specific appendices)
- Urine collection for urinalysis
- Administration of C-SSRS
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight and height)
- Physical and neurological examinations
- Clinical assessments: CDR, calculation of CDR-SB, NPI-Q, GDS, FAS, MMSE, and assessment of clinical diagnosis and clinician judgment of symptoms
  NOTE*: For each participant, the CDR and assessment of clinical diagnosis should be administered by the same experienced clinician at all visits. Whenever possible, the CDR rater should not be involved in other clinical assessments (e.g., MMSE, FAS, GDS, NPI-Q) or in cognitive testing*
- DIAN-TU Harmonized Cognitive Battery (per Section 6.1.14.2)
- 12-lead ECG
- **MRI to be performed on 1st day** and uploaded immediately to ensure reading obtained prior to randomization and dosing. This MRI includes safety MRI sequences. MRI findings may affect eligibility for the trial for some drug arms. MRI should be performed before lumbar puncture (if on the same day) or scheduled to be on a different day than the lumbar puncture
- Lumbar Puncture (LP) for CSF collection should be performed at approximately 8 AM local time, under fasting conditions (water is allowed and encouraged). Site staff should contact the participant 24 to 48 hours after the LP to assess for adverse effects of the LP
- PET imaging (see each drug-specific appendix for details)
- **See each drug-specific appendix for additional assessments which may be required**
- Final verification that all inclusion and no exclusion are met (including receipt of MRI read)
- Randomization in IWRS system
- Supplemental drug-specific informed consent reviewed and signed, if not a stand-alone consent
- Reminder regarding ARC smartphone-based cognitive assessment completion
- Study drug dosing and post-dose monitoring/evaluation as specified in each drug-specific appendix

After all baseline measures have been completed and adherence to inclusion and exclusion criteria has been verified, randomization and assignment to study drug arm is completed using the IWRS during this visit. Randomization cannot occur until results of baseline (V2) CDR are entered into the IWRS system. After randomization, participant and legally authorized representative (if the participant is cognitively impaired) should review and sign the supplemental drug-specific informed consent form (if applicable); study staff should be available to answer all questions regarding the study. Study drug should not be administered

until MRI is read to confirm eligibility (if required for specific study drug, e.g., number of microhemorrhages), pregnancy test is confirmed negative, and any other drug-specific inclusion/exclusion criteria have been verified.

6.3.4 Double-blind Treatment Period

The double-blind treatment period for each study drug arm will vary based on when the participant was enrolled and may last from 4 up to 7 years (364 weeks [V93]) or until early termination, whichever is sooner. Participants will continue treatment with the assigned study drug until every participant randomized to that study drug arm has received a minimum of 4 years (208 weeks) of treatment or is withdrawn. After the double-blind treatment period is completed, participants may be eligible to continue treatment in an open-label extension if the study drug arm demonstrates a potential for clinical benefit.

Location: Monthly procedures/contacts may be accomplished at/by the DIAN-TU site, at the participant's home, or other trial-identified location with the trial-designated home health nurse. Annual visits will take place at DIAN-TU qualified sites.

Time/Timing: Generally every 4 weeks (± allowed visit window) until the last participant in a study drug arm has completed their year 4 visit, or the study drug arm has been terminated. Some drug arms may require a different frequency of visits based on study drug administration requirements; these will be specified in the drug-specific appendices including any allowable visit windows.

Visit duration depends on specific visit and study drug (e.g., infusion time, observation time after infusion). Note that annual visits may take place over 3 to 4 days. For participants who live near the study site, these visit procedures may be scheduled over a longer time period of up to 2 weeks.

Procedures: **See each drug-specific appendix for the specific assessments that are required at each visit.** Procedures may include any of the following:

- Medical/treatment history, including:
  - Concomitant medications
  - Assessment /recording of adverse events
- Urine pregnancy testing, if applicable
- Laboratory sample collection (e.g., drug-specific tests, stored plasma and/or serum, and clinical safety assessment as outlined in the drug-specific appendices)
- Administration of C-SSRS
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight and height)
- Physical and neurological examinations

- Clinical assessments:
  - CDR, including calculation of CDR-SB
  - NPI-Q
  - GDS
  - FAS
  - MMSE
  - Assessment of clinical diagnosis and clinician judgment of symptoms

  NOTE*: For each participant, the CDR and assessment of clinical diagnosis should be administered by the same experienced clinician at all visits. Whenever possible, the CDR rater should not be involved in other clinical assessments (e.g., MMSE, FAS, GDS, NPI-Q) or in cognitive testing.*
- 12-lead ECG
- DIAN-TU Harmonized Cognitive Battery
- ARC smartphone-based cognitive assessment
- MRI (should be performed before lumbar puncture, if on the same date)
- Lumbar Puncture (LP) for CSF collection should be performed in the morning, at approximately 8 am local time, under fasting conditions (water is allowed and encouraged). Site staff should contact the participant 24 to 48 hours after the LP to assess for adverse effects of the LP
- PET imaging
- Study drug administration
- Site phone call (not required after all off-site visits but direct site-participant contact should occur at least once every 3 months throughout the study): the DIAN-TU site coordinator calls participant and addresses any concerns, discusses scheduling of safety MRI and/or next visits, and encourages compliance

6.3.5 End-of-Treatment / Safety Follow-up Visit

The double-blind treatment period for each participant may vary based on when the participant was enrolled and may last from 4 (208 weeks [V54]) up to 7 years (364 weeks [V93]) or until early termination, whichever is sooner. Participants will continue treatment with the assigned study drug until every participant randomized to the study drug arm has received a minimum of 4 years (208 weeks) of treatment or is withdrawn, at which time study treatment will be discontinued for all participants in the study drug arm and all participants should be scheduled for an end-of-treatment/safety follow-up visit, if/as specified in the drug-specific appendices.

Location: Procedures/contacts may be accomplished at the DIAN-TU site or participant's home or other trial-identified location with the trial-designated home health nurse.

Timing: The end of treatment/safety follow-up visit should be performed approximately 12 weeks (± 7 days) after the participant's last dose of double-blind treatment, or as specified in the drug-specific appendices. The sequence and timing of visit procedures is very important and are detailed in the *Global Manual of Operations*.

*Procedures **may** include any of the following:*

- Concomitant Medications
- Adverse Event Assessment
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight)
- Administration of C-SSRS
- Laboratory sample collection (e.g., drug-specific tests, and clinical safety assessment as outlined in the drug-specific appendices)
- Urine collection for urinalysis

Any procedures done after the last dose, but before the safety follow-up visit, may not need to be repeated. **See each drug-specific appendix for the specific assessments that are required at each visit.**

6.3.6 Open-label Extension

Study drug arms that demonstrate a potential for clinical benefit may offer an open-label extension (OLE) period at the discretion of the sponsor and respective pharma partner.

Participants from concurrent negative arms may have the option of enrolling into the OLE of the study drug arm with positive results after at least a steady-state washout (five drug PK half-lives) from their last double-blind dose.

All OLE participants and study sites will be kept blinded to prior treatment assignment until the end of OLE to protect study integrity.

Any mutation carrier who participated in the placebo-controlled portion of the trial in which the investigator and sponsor deem treatment is not contraindicated for safety and is capable of receiving drug and appropriate clinical safety assessments, is eligible.

Written informed consent must be obtained from the participant, study partner (if applicable), and/or by the participant's legally authorized representative accordingly (Section 6.1.1).

Location: Monthly procedures/contacts during the OLE may be accomplished at the DIAN-TU site, at the participant's home, or other trial-identified location with the trial-designated home health nurse. Annual visits will take place at the host DIAN-TU site.

Time/Timing: Every 4 weeks (± allowed visit window) beginning at dosing restart; refer to the drug-specific appendices for allowable visit windows.

Visit duration depends on procedures required at the visit and study drug administration requirements (e.g., infusion time, observation time after infusion). Note that annual visits may take place over 2 to 3 days. For participants who live near the study site, these visit procedures may be scheduled over a longer time period of up to 2 weeks.

Procedures: **See each drug-specific appendix for the specific assessments that are required at each visit.** Procedures may include any of the following however biomarker assessments and cognitive batteries will be performed during OLE at the discretion of the sponsor and pharma

partner contingent upon the individual measure demonstrating continued utility in OLE based on the results of the double-blind period of the study.

- Obtain informed consent. Participants who wish to join the OLE may sign consent once a decision regarding the initiation of an OLE has been communicated by the sponsor, and an approved OLE ICF is available at the site
- Confirmation of having a trial-eligible pathogenic DIAD variant at the time of entry into OLE
- Medical/treatment history, including:
  - Concomitant medications
  - Assessment /recording of adverse events
- Urine pregnancy testing, if applicable
- Laboratory sample collection for clinical laboratory tests and blood-based biomarker measures (e.g., drug-specific tests, stored plasma and/or serum) per drug-specific appendices, if/as determined by the sponsor and pharma partner
- Administration of C-SSRS
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight and height)
- Physical and neurological examinations
- Clinical assessments:
  - CDR including calculation of CDR-SB
  - NPI-Q
  - GDS
  - FAS
  - MMSE
  - Assessment of clinical diagnosis and clinician judgment of symptoms.

  NOTE*: For each participant, the CDR and assessment of clinical diagnosis should be administered by the same experienced clinician at all visits. Whenever possible, the CDR rater should not be involved in other clinical assessments (e.g., MMSE, FAS, GDS, NPI-Q) or in cognitive testing.*
- 12-lead ECG
- Cognitive testing, if/as determined by the sponsor and pharma partner
- PET imaging:
  - [^{11}C]PiB
  - FDG-PET (participant should be fasting 4 hours prior to FDG-PET)
  - [^{18}F]AV-1451 or [^{18}F]MK-6240
- LP (CSF collection)
- MRI (should be performed before LP if on the same date)
- Administer study drug
- Coordinator phone call: Site study coordinators should call participants either during or within two weeks after OLE V2, OLE V3 and OLE V4. For OLE V5 and subsequent home

visits, coordinator calls can be made with less frequency at the discretion of the coordinator and participant, but should occur at least every 3 months

6.3.7 Early Termination Visit and Post-treatment Follow-up Period

If a participant withdraws, is terminated from the study prior to completion of a treatment period, or is in a study drug arm that is stopped prior to the end of the treatment period, every effort should be made to schedule an early termination visit. PET imaging studies may be omitted if early termination occurs less than 6 months after the previous PET imaging or if precluded by local regulations/dosimetry limits. Other procedures may also be eliminated on a case-by-case basis, as determined by the sponsor or if not required based on the study drug arm procedures or study period.

Any participant that meets study drug discontinuation criteria per Section 4.4.1 (excluding participants who are known mutation negative) will be encouraged to continue participation in any of the scheduled clinical, cognitive, and/or biomarker assessments that are able to be performed even though dosing has concluded. The determination of which assessments to be attempted/completed will be decided with the site principal investigator and sponsor based on the participant's capabilities, the benefit to the study, and the risk associated with continued participation at the time of study drug discontinuation. The level of continued participation may change if/as the participant's status changes.

Location: DIAN-TU site or at the participant's home or other trial-identified location with the trial-designated home health nurse

Time/Timing: The early termination visit may occur at any time during the study. Approximately a 3- to 4-day visit. For participants who live near the study site, these visit procedures may be scheduled over a longer time period of up to 2 weeks.

Procedures: **See each drug-specific appendix for the specific assessments that are required at each visit.** Procedures may include any of the following:

- Medical/treatment history, including:
  - Concomitant medications
  - Assessment /recording of adverse events
- Laboratory sample collection (drug-specific tests, stored plasma and/or serum, and clinical safety assessment)
- Administration of C-SSRS
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight and height)
- Physical and neurological examinations
- Clinical assessments:
  - CDR including calculation of CDR-SB
  - NPI-Q
  - GDS

- FAS
- MMSE
- Assessment of clinical diagnosis and clinician judgment of symptoms.

***NOTE**: For each participant, the CDR and assessment of clinical diagnosis should be administered by the same experienced clinician at all visits. Whenever possible, the CDR rater should not be involved in other clinical assessments (e.g., MMSE, FAS, GDS, NPI-Q) or in cognitive testing.*

- Cognitive testing
- MRI (structural and functional) should be performed before lumbar puncture, if on the same date
- Lumbar Puncture (LP) for CSF collection should be performed in the morning, at approximately 8 am local time, under fasting conditions (water is allowed and encouraged). Site staff should contact the participant 24 to 48 hours after the LP to assess for adverse effects of the LP.
- PET imaging
- Drug reconciliation as specified in each drug-specific appendix

6.4 Termination of the Study

The sponsor may terminate the study or study-drug arm, and CRI period at any time. Furthermore, if it becomes apparent that participant enrollment is unsatisfactory with respect to quantity or quality, or that data recording is inaccurate or incomplete on a chronic basis, the sponsor has the right to terminate the study and remove all study materials from the investigational site. A written statement will be provided to the investigator, IRB/IEC, and regulatory authorities, if required. If any SAEs are reported as part of the reason for early termination of the study, all documentation relating to the event(s) reported to regulatory authorities must be obtained and filed appropriately. The DSMB may recommend termination of the study or study drug arm but final decisions will be made by the sponsor. Any time a study drug arm is not recruiting participants, opening recruitment to CRI period will be considered.

7 SAFETY AND ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a participant administered study drug, whether or not considered drug related. An adverse event can be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to

study drug. An adverse event can arise from any use of the drug and from any route of administration, formulation, or dose including an overdose.

Any medical condition that is present at the time the participant is consented but does not deteriorate should not be reported as an AE. However, if it deteriorates or worsens significantly at any time during the study, it should be recorded as an AE.

Clinically meaningful (for a given participant) changes in physical examination findings and abnormal objective test findings, e.g., laboratory, vital signs, ECG, imaging (e.g., definite new ARIA changes) should also be recorded as AEs. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

1. Test result is associated with accompanying symptoms or is of clinical concern
2. Test result requires additional diagnostic testing or medical/surgical intervention
3. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
4. Test result leads to any of the outcomes included in the definition of a SAE

Merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria 2 above for reporting as an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

***NOTE**: The following are not considered AEs or SAEs:*

- **Preplanned surgeries or procedures:** Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.
- **Elective surgeries or procedures:** Elective procedures performed where there is no change in the participant's medical condition should not be recorded as AEs, but should be documented in the participant's source documents. Complications resulting from an elective surgery should be reported as AEs or SAEs (depending on the severity).
- **Insufficient clinical response (lack of efficacy):** Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The principal investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

7.1.2 Serious Adverse Event

If any adverse event meets any of the following criteria in the view of either the investigator or sponsor, it is to be reported to the safety group as a serious adverse event (SAE) within 24 hours of occurrence or notification of the site:

- **Death of participant.** An event that results in the death of a participant.
- **Life-threatening.** An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
- **Inpatient hospitalization**. An event that results in the admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
- **Prolongation of existing hospitalization.** An event that occurs while the study participant is hospitalized and prolongs the participant's hospital stay.
- **A persistent or significant disability/incapacity.** An event that results in a condition that substantially interferes with the activities of daily living of a study participant. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (*e.g.*, sprained ankle).
- **Important medical event requiring medical or surgical intervention to prevent serious outcome.** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the participant and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of participant, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such 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.
- **Congenital anomaly/birth defect**. An anomaly detected at or after birth, or any anomaly that results in fetal loss.

7.2 Adverse Event (AE) Severity

The intensity of the AE will be rated by the investigator as mild, moderate, or severe using the following criteria:

Mild: an event that is transient and easily tolerated by the participant; requires minimal or no treatment and does not interfere with the participant's daily activities.

Moderate: an event that causes the participant discomfort and may cause some interference in the participant's usual activities.

Severe: an event that causes considerable interference with the participant's usual activities, may require drug therapy or other treatment, and may be incapacitating or life-threatening.

7.3 Relationship to Study Drug

The relationship of an AE to study drug, imaging agents (e.g., [^{11}C]PiB and ^{18}F tracers) and or study procedures should be assessed by the site principal investigator using the following guidance:

Definite. An event, including laboratory test abnormality, which:

a. Occurs within a reasonable temporal sequence to administration of study drug,
b. Cannot be explained by concurrent disease or other drugs or chemicals
c. Improves or disappears on stopping or reducing study drug (dechallenge)
d. Reappears on repeated exposure to study drug (rechallenge)
e. Is an unusual event that is known to be associated with the drug or this class of compound, and cannot be explained by other therapy or the participant's physical condition.

Probable/Likely. An event, including laboratory test abnormality, which:

a. Occurs within a reasonable temporal sequence to administration of study drug,
b. Unlikely to be attributed to concurrent disease or other drugs or a clinically reasonable response on withdrawal (dechallenge)
c. Rechallenge was not attempted.

Possible. An event, including laboratory test abnormality, which:

a. Occurs within a reasonable temporal sequence to administration of study drug, but
b. Could also be explained by concurrent disease or other drugs or chemical
c. Information on drug withdrawal may be lacking or unclear.

Unlikely. An event, including laboratory test abnormality, which:

a. Occurs with a temporal relationship to administration of study drug which makes a causal relationship improbable, and
b. In which other drugs, chemicals or underlying disease provide plausible explanations.

Definitely Not. An event, including laboratory test abnormality, which is known to be associated with the participant's clinical condition, or with other medication taken by the participant.

7.4 Adverse Event Collection Period

All AEs reported from the time that informed consent is obtained until 30 days following the last dose of study drug (or 30 days after the last visit if in the CRI period only) will be collected, whether elicited or spontaneously reported by the participant. Adverse events should be collected at End of Study and Early Termination visits even if these visits occur more than 30 days after last dose of study drug. Serious adverse events considered related to study drug or procedures should be reported even if they occur more than 30 days after the last dose of study drug.

At every study visit, participants will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

7.5 Adverse Event Reporting

The investigator will monitor each participant for clinical and laboratory evidence of AEs on a routine basis throughout the study. Conditions present at baseline will be documented. Deterioration or worsening of conditions present at baseline should be reported as an AE. All AEs reported or observed during the study will be recorded in the AE eCRF. Information to be collected includes the type of event, date of onset, investigator-specified assessment of severity and relationship to study drug, date of resolution of the event, and seriousness. Treatments for AEs will be recorded on the concomitant medication eCRF. AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs, whether serious or non-serious, should be followed to resolution or until the AE is determined by the investigator not to be clinically significant or to be chronic or stable. Medical Dictionary for Regulatory Activities (MedDRA®) will be used to code all AEs.

7.6 Serious Adverse Event Reporting

The principal investigator must report to IQVIA Safety (formerly known as Quintiles) any AE considered serious by the investigator, or which meets any of the specified criteria in Section 7.1.2. Refer to each drug-specific appendix for drug-specific AE and SAE reporting. The initial report must be submitted within 24 hours from the time site personnel first learns about the event by entry into the study's electronic data capture (EDC) system; in cases where a back-up submission method is needed the site must submit SAE documentation to the project mailbox: QLS_WashU@quintiles.com.

Contact information for IQVIA Safety:

IQVIA SAFETY:
Toll-free for US sites:
Phone: (866) 599-1341
Fax: (866) 599-1342
For all sites/international:
+1 973-659-6677 *or*
+1-570-819-8565 (alternative number)

Additional contact information is detailed in the *Global Manual of Operations*.

The reporting should include completion of the eCRF Adverse Event Form with Serious event indicated as Yes, and verification of current data entry in the eCRFs or de-identified source

documents for the demographics page(s), medical history page(s), AE page(s) and concomitant medication page(s). If the participant is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary should be faxed to IQVIA Safety as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the investigator unless the event meets a protocol-specified discontinuation criterion. All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the participant to be stable.

The sponsor or its designee will be responsible for reporting SAEs to FDA, European Medicines Agency (EMA) and other relevant regulatory authorities accordingly to local regulatory requirements. Sites are responsible for reporting to their local ethics committees /IRBs per their reporting requirements and/or local laws.

7.7 Pregnancy Reporting

Cases of pregnancy that occur during maternal or paternal exposures to study drug or within 5 half-lives following last dose of study drug should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation. Sites should report pregnancies to IQVIA Safety in the same manner and timing as for Serious Adverse Events specified in Section 7.6.

7.8 Hy's Law

Suspected Hy's law cases should be reported to IQVIA Safety in the same manner and timing as for Serious Adverse Events specified in Section 7.6.

7.9 Adverse Events of Special Interest

Refer to the drug-specific appendices for drug-specific reporting for adverse events of special interest (AESI). Sites should report an AESI to IQVIA Safety in the same manner and timing as for Serious Adverse Events specified in Section 7.6.

7.10 Data Safety Monitoring Board (DSMB)

Unblinded data from study drug arms on safety-related endpoints (clinical laboratory test results, ECGs, MRI findings, cognitive and clinical endpoint results), SAEs, and AESIs will be reviewed quarterly by the DSMB. Complete details are available in the DSMB charter.

8 STATISTICAL PLAN

The data collected in the CRI period may be used for analysis in the respective drug arm under which participants are randomized and treated.

A detailed drug-specific statistical analysis plan will be used for interim and final efficacy analyses and for the biomarker interim analyses for each drug arm.

8.1 Descriptive Statistics

Descriptive statistics will be provided for safety and efficacy variables at each time point collected by treatment groups and across combined placebo groups. Continuous variables (e.g., biomarker values) will be summarized using the number of observations, mean, standard deviation (SD), minimum, lower quartile, median, upper quartile, and the maximum. Categorical variables (e.g., presence of absence of an *APOE ε4* allele) will be summarized using the number and percentage in each category.

8.2 Safety Analysis

Safety analysis will be drug-specific and in general include all participants who consent to participate and are randomized to receive any study-related drugs or placebo and will be reported to an independent Data Safety Monitoring Board (DSMB) for regular reviews. The following are major safety endpoints that will be analyzed: treatment-emergent adverse events (TEAE), serious treatment-emergent AEs, serious drug-related treatment-emergent AEs, treatment-emergent AEs that lead to discontinuation of the study, treatment-emergent AEs resulting in death, safety MRIs, laboratory parameters, vital signs and physical examinations. Adverse event reporting will include the severity, onset, duration, relief measures, outcome, and relationship to study drug. Adverse events will be classified using MedDRA preferred terms. Adverse events noted on MRI scans, including ARIA, will be analyzed as will adverse events noted as significant changes or new abnormalities in vital signs, clinical laboratory test values or ECGs.

8.3 Biomarker Endpoint Statistical Analysis, Power and Sample Size Justification

Each drug that enters the DIAN-TU platform trial will have biomarker defined interim analyses. The goal of the interim analyses is to stop or adjust a treatment that is not demonstrating sufficient efficacy on the target biomarker. Each study drug arm will have a target biomarker, a target biomarker analysis, and a remediation plan should the biomarker analysis demonstrate lack of success. The remediation plan will include dose-adjustment strategies, if appropriate, to maximize the efficacy, if the tolerability and safety profile is acceptable. If no adjustments are possible, then failing the biomarker interim will lead to stopping the regimen for futility. Each drug-specific appendix will detail the biomarker interim analysis. The biomarker interim analyses will be used for dose-adjustment, remediation, or stopping a study drug arm for futility and will not be used to stop the study for efficacy on the primary endpoint.

Interim biomarker analyses will be conducted for each study drug arm to assess whether the active study drug is engaging its biological target. The timing of the interim biomarker analyses may vary for each study drug arm. At each interim, an analysis will be conducted for the biomarker endpoints. Pre-specified definitions for early termination for futility will be drug-

specific and based on collection of appropriate biomarker assessments following sufficient drug exposure. Details about the interim biomarker analyses are described in each drug-specific protocol appendix and SAP appendices.

8.4 Primary Efficacy Endpoint Statistical Analysis, Power and Sample Size Justification

The primary efficacy endpoint may vary across study drug arms. For each study drug, the corresponding primary efficacy endpoint, the statistical analysis, and the power and sample size justification will be presented in the drug-specific appendix.

The modified intent-to-treat (mITT) population is defined as all participants who will be randomized, treated, and assessed for their primary cognitive outcomes at least once after the baseline assessment. Refer to the drug-specific appendices for details as individual drug arms may further define their respective analysis populations.

All efficacy analyses will be conducted on the mITT population and eligible external controls, if deemed necessary; as specified in the drug-specific appendices.

Final analysis will be pre-specified in the SAP and/or drug-specific SAP appendices.

8.5 OLE Outcomes

Analyses for outcomes in any OLE period will be completed for the outcomes described in each drug-specific appendix.

9 DATA HANDLING AND RECORD KEEPING

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories.

Electronic Case Report Forms (eCRFs) or appropriate access to the electronic data capture (EDC) system by investigator-delegated site personnel. These forms and system(s) will be used to transmit information collected during the study to the sponsor and designee, those in collaboration with the sponsor for the study, and regulatory authorities, as applicable. All data should be entered into the EDC system in a timely manner as specified in the *Global Manual of Operations*. All information entered in the EDC must also be reflected in the participant source documents.

The principal investigator will review the source documentation and eCRFs (EDC) for completeness and accuracy and sign/date via electronic signature in the system where indicated.

The investigator will retain all essential documents until at least two years after the last approval of a marketing application in an International Conference on Harmonisation (ICH)

region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the investigator and/or institution to notify the sponsor in writing of any change in record retention, i.e., transfer of responsibility in the event of relocation, retirement, etc. It is the responsibility of the sponsor or designee to inform the investigator/institution as to when these documents no longer need to be retained.

10 STUDY MONITORING, AUDITING AND INSPECTING

The participant data (EDC and source documents) will be reviewed for completeness, legibility and acceptability by the sponsor or designee/representatives. The sponsor and designee/representatives will be allowed access to all source documents in order to verify all EDC entries. Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, participant diaries, pharmacy dispensing and other records, recorded data from automated instruments, magnetic media, x-rays, etc.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data documents. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor and applicable regulatory authorities access to all study records. The investigator should promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

All aspects of the study will be carefully monitored, by the sponsor or designee, for compliance with applicable government regulations with respect to current GCP and current standard operating procedures.

The monitor will visit the investigator and study facility at periodic intervals, in addition to maintaining pertinent telephone, e-mail, and letter correspondence contact. The monitor will maintain current knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

10.1 Protocol Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes outlined within the protocol. The investigator or designee must document and explain in the participant's source documentation any deviation from the IRB/IEC approved protocol. Protocol deviations will also be documented by the clinical monitor throughout the course of the monitoring visit and/or site management. The site must notify their IRB/IEC of required and/or significant protocol deviations in a timely manner in accordance with their policies and any local regulations.

10.2 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of Serious Adverse Events according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to his/her IRB/IEC as appropriate. The investigator also agrees to provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH Guidance E6 8.2 and Title 21 of the Code of Federal Regulations (CFR) by providing the following essential documents, including but not limited to:

- An original investigator-signed Investigator's Statement of Agreement page of the protocol.
- An IRB/IEC-approved ICF, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the participant/legal guardian/representative.
- IRB/IEC approval.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572 for all US sites. Comparable document(s) may be required for non-US sites at the discretion of the sponsor or designee.
- Curriculum vitae (CV) for the principal investigator and each sub-investigator listed on Form FDA 1572. Current licensure should be noted on the CV and/or included. CVs should be signed and dated by the principal investigators and sub-investigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

11 ETHICAL CONSIDERATIONS

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 parts 50, 54, 56, and 312 and International Conference for Harmonization guidelines), applicable government regulations and Institutional research policies and procedures. At each participating DIAN-TU site, the principal investigator will submit this protocol and any amendments, Investigator's Brochure, informed consent, recruitment materials, etc., to the properly constituted IRB or IEC, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IEC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision

will be provided to the sponsor or its designee before commencement of this study. Each DIAN-TU site will be responsible for obtaining appropriate approvals for satellite sites and other providers (e.g., home health nurses, infusion sites) used by their participants for study activities, as applicable.

Any amendments to the protocol and informed consent will require IRB/IEC approval prior to implementation of any changes made to the study design.

The investigator agrees that the study will be conducted according to the principles of the ICH E6 Guideline on GCP and the World Medical Association Declaration of Helsinki. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

The written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki, 21 CFR Part 50.25, ICH GCP, and in accordance with any local regulations. The ICF must be approved by the clinical site's IRB/IEC and be acceptable to Washington University in St. Louis.

12 STUDY FINANCES

Investigators are required to provide financial disclosure information to allow the sponsor or designee to submit the complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

The sponsor is not financially responsible for further testing/treatment of any medical condition that may be detected during the baseline process. In addition, in the absence of specified arrangements, the sponsor is not financially responsible for further treatment of the participant's disease.

13 PUBLICATION PLAN

The DIAN-TU committee on data sharing and publications will establish policies and guidelines for DIAN-TU data sharing and oversight of publications using DIAN-TU data. Pharma partners will be consulted when issues specific to their study compounds arise, but the DIAN-TU retains the right to publish the results of this trial consistent with the policies of the DIAN-TU and any regional regulatory requirements.

14 REFERENCES

Aisen , P.S., Cummings J.L., Sperling RA. (2016). “TPC-PAD: Using Run-In Data for Screen Failure Reduction.” Alzheimer's & Dementia 12(7):P372.

Bateman, R.J., C. Xiong, et al. (2012). "Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease." N Engl J Med 367(9): 795-804.

Barthélemy, N.R., Li, Y., et al. (2020). A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer’s disease. Nat Med 26, 398–407.

Benzinger, T. L., T. Blazey, et al. (2013). "Regional variability of imaging biomarkers in autosomal dominant Alzheimer's disease." Proc Natl Acad Sci U S A 110(47): E4502-4509.

Blom, E. S., V. Giedraitis, et al. (2009). "Rapid progression from mild cognitive impairment to Alzheimer's disease in participants with elevated levels of tau in cerebrospinal fluid and the APOE epsilon4/epsilon4 genotype." Dement Geriatr Cogn Disord 27(5): 458-464.

Braak, H. and E. Braak (1995). "Staging of Alzheimer's disease-related neurofibrillary changes." Neurobiol Aging 16(3): 271-278; discussion 278-284.

Buchhave, P., L. Minthon, et al. (2012). "Cerebrospinal fluid levels of beta-amyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia." Arch Gen Psychiatry 69(1): 98-106.

Buerger, K., M. Ewers, et al. (2006). "CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease." Brain 129(Pt 11): 3035-3041.

Chetelat, G., V. L. Villemagne, et al. (2012). "Accelerated cortical atrophy in cognitively normal elderly with high beta-amyloid deposition." Neurology 78(7): 477-484.

Craig-Schapiro, R., R. J. Perrin, et al. (2010). "YKL-40: a novel prognostic fluid biomarker for preclinical Alzheimer's disease." Biol Psychiatry 68(10): 903-912.

Data on file (2018). Romano G. Preliminary analyses of data from ongoing trial of atabecestat in preclinical Alzheimer's Disease.

Doraiswamy, P. M., R. A. Sperling, et al. (2012). "Amyloid-beta assessed by florbetapir F 18 PET and 18-month cognitive decline: A multicenter study." Neurology 79: 1633-1644.

Duyckaerts, C., J. P. Brion, et al. (1987). "Quantitative assessment of the density of neurofibrillary tangles and senile plaques in senile dementia of the Alzheimer type. Comparison of immunocytochemistry with a specific antibody and Bodian's protargol method." Acta Neuropathol 73(2): 167-170.

Fagan, A. M., D. Head, et al. (2009). "Decreased cerebrospinal fluid Abeta(42) correlates with brain atrophy in cognitively normal elderly." Ann Neurol 65(2): 176-183.

Fagan, A. M., C. M. Roe, et al. (2007). "Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults." Arch Neurol 64(3): 343-349.

Fagan, A. M., C. Xiong, et al. (2014). "Longitudinal change in CSF biomarkers in autosomal-dominant Alzheimer's disease." Sci Transl Med 6(226): 226ra230.

Fagan AM, Mintun MA, Mach RH, Lee S-Y, Dence CS, Shah AR, LaRossa G, Spinner ML, Klunk WE, Mathis CA, DeKosky ST, Morris JC, Holtzman DM Inverse relation between in vivo amyloid imaging load and CSF Aβ42 in humans, Annals of Neurology, 2006; 59:512-519.

Gaetani L., Blennow K., et al. (2019). "Neurofilament light chain as a biomarker in neurological disorders." J Neurol Neurosurg Psychiatry 90(8): 870-881.

Gordon, Brian A., et al. "Tau PET in autosomal dominant Alzheimer's disease: relationship with cognition, dementia and other biomarkers." Brain 142.4 (2019): 1063-1076.

Hansson, O., H. Zetterberg, et al. (2006). "Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study." Lancet Neurol 5(3): 228-234.

Hassenstab, J. et al. (2015). "Absence of practice effects in preclinical Alzheimer's disease." Neuropsychology 29: 940–948.

Hesse, C, L. Rosengren, et al. (2000). "Cerebrospinal fluid markers for Alzheimer's disease evaluated after acute ischemic stroke." J Alzheimers Dis 2(3-4): 199-206.

Hostetler, E. D., A. M. Walji, Z. Zeng, P. Miller, I. Bennacef, C. Salinas, B. Connolly, L. Gantert, H. Haley, M. Holahan, M. Purcell, K. Riffel, T. G. Lohith, P. Coleman, A. Soriano, A. Ogawa, S. Xu, X. Zhang, E. Joshi, J. Della Rocca, D. Hesk, D. J. Schenk and J. L. Evelhoch (2016). "Preclinical Characterization of 18F-MK-6240, a Promising PET Tracer for In Vivo Quantification of Human Neurofibrillary Tangles." J Nucl Med 57(10): 1599-1606.

Ivnik R, Smith G, Petersen R, Boeve B, Kokmen E, Tangalos E. (2000) "Diagnostic accuracy of four approaches to interpreting neuropsychological test data." Neuropsychology. 14(2):163-177.

Klein G, Delmar P, et al. (2019). Gantenerumab reduces amyloid-β plaques in patients with prodromal to moderate Alzheimer's disease: a PET substudy interim analysis. Alzheimers Res Ther 11(1):101.

Klein G, Delmar P, et al. Thirty-Six-Month Amyloid Positron Emission Tomography Results Show Continued Reduction in Amyloid Burden with Subcutaneous Gantenerumab. J Prev Alzheimers Dis. 2021;8(1):3-6.

Landau, S. M., D. Harvey, et al. (2010). "Comparing predictors of conversion and decline in mild cognitive impairment." Neurology 75(3): 230-238.

Lewczuk P, Matzen A, Blennow K, Parnetti L, Molinuevo JL, Eusebi P, Kornhuber J, Morris JC, Fagan AM. Cerebrospinal Fluid Aβ42/40 Corresponds Better than Aβ42 to Amyloid PET in Alzheimer's Disease. Journal of Alzheimer's Disease. 2016 Nov 19;55(2):813-822.

Li, G., I. Sokal, et al. (2007). "CSF tau/Aβ42 ratio for increased risk of mild cognitive impairment: a follow-up study." Neurology 69(7): 631-639.

Lohith, T., I. Bennacef, C. Sur, R. Declercq, K. Serdons, G. Bormans, E. Hostetler, K. Van Laere, R. Vandenberghe and A. Struyk (2017). "Quantification of [18F] MK-6240, a new PET tracer targeting human neurofibrillary tangles (NFTs) in brain of healthy elderly and participants with Alzheimer's disease." Journal of Nuclear Medicine 58(supplement 1): 277-277.

Lohith, T., I. Bennacef, Z. Zeng, M. Holahan, M. Koole, K. Van Laere, C. Sur, A. Struyk, A. Walji and E. Hostetler (2016). "Preclinical evaluation and first-in-human dosimetry of [18F] MK-6240, a new PET tracer for in vivo quantification of human neurofibrillary tangles." Journal of Nuclear Medicine 57(supplement 2): 125-125.

Mattsson-Carlgren N, Andersson E, Janelidze S, et al. Aβ deposition is associated with increases in soluble and phosphorylated tau that precede a positive Tau PET in Alzheimer's disease. *Sci Adv*. 2020;6(16):eaaz2387. Published 2020 Apr 15. doi:10.1126/sciadv.aaz2387

McKhann, G. M., D. S. Knopman, et al. (2011). "The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." Alzheimers Dement 7(3): 263-269.

Mintun, M. A., G. N. Larossa, et al. (2006). "[11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease." Neurology 67(3): 446-452.

Moonis, M., J. M. Swearer, et al. (2005). "Familial Alzheimer disease: decreases in CSF Abeta42 levels precede cognitive decline." Neurology 65(2): 323-325.

Morris, J. C., C. M. Roe, et al. (2009). "Pittsburgh Compound B Imaging and Prediction of Progression From Cognitive Normality to Symptomatic Alzheimer Disease." Archives of Neurology 66(12): 1469-1475.

Neelamegam, R., D. L. Yokell, P. A. Rice, S. Furumoto, Y. Kudo, N. Okamura and G. El Fakhri (2017). "A report of the automated radiosynthesis of the tau positron emission tomography radiopharmaceutical,[18F]-THK-5351." Journal of Labelled Compounds and Radiopharmaceuticals 60(2): 140-146.

Nelson, P. T., I. Alafzoff, et al. (2012). "Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature." J Neuropathol Exp Neurol 71(5): 362-381.

Novak, G., J.R. Streffer, et al. (2020). "Long-term safety and tolerability of atabecestat (JNJ-54861911), an oral BACE1 inhibitor, in early Alzheimer's disease spectrum patients: a randomized, double-blind, placebo-controlled study and a two-period extension study." Alzheimer's Research & Therapy 12(58).

Ossenkoppele, Rik et al. (2016). "Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease." Brain 139(Pt 5): 1551-1567.

Ost, M., K. Nylen, et al. (2006). "Initial CSF total tau correlates with 1-year outcome in patients with traumatic brain injury." Neurology 67(9): 1600-1604.

Pablos-Méndez A, Barr RG, Shea S. (1998). "Run-in periods in randomized trials: implications for the application of results in clinical practice." JAMA 279(3):222-225.

Portelius, E., J. Fortea, et al. (2012). "The amyloid-beta isoform pattern in cerebrospinal fluid in familial PSEN1 M139T- and L286P-associated Alzheimer's disease." Mol Med Report 5(4): 1111-1115.

Preische, O, Schultz S, et al. (2019). "Serum Neurofilament Dynamics Predicts Neurodegeneration and Clinical Progression in Presymptomatic Alzheimer's Disease." Nature Medicine 25: 277–283.

Price, J. L., D. W. McKeel, Jr., et al. (2009). "Neuropathology of nondemented aging: presumptive evidence for preclinical Alzheimer disease." Neurobiol Aging 30(7): 1026-1036.

Price, J. L. and J. C. Morris (1999). "Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease." Ann Neurol 45(3): 358-368.

Ringman, J. M., G. Coppola, et al. (2012). "Cerebrospinal Fluid Biomarkers and Proximity to Diagnosis in Preclinical Familial Alzheimer's Disease." Dement Geriatr Cogn Disord 33(1): 1-5.

Ringman, J. M., S. G. Younkin, et al. (2008). "Biochemical markers in persons with preclinical familial Alzheimer disease." Neurology 71(2): 85-92.

Ryman, D. C., N. Acosta-Baena, et al. (2014). "Symptom onset in autosomal dominant Alzheimer disease: a systematic review and meta-analysis." Neurology 83(3): 253-260.

Schechtman K.B., Gordon M.E. (1993). "A comprehensive algorithm for determining whether a run-in strategy will be a cost-effective design modification in a randomized clinical trial." Statistics in Medicine 12(2):111-128.

Schindler SE, Jasielec MS, Weng H, Hassenstab JJ, Grober E, McCue LM, Morris JC, Holtzman DM, Xiong C, Fagan AM. Neuropsychological measures that detect early impairment and decline in preclinical Alzheimer disease. Neurobiology of Aging. 2017 56:25-32.

Snider, B. J., A. M. Fagan, et al. (2009). "Cerebrospinal fluid biomarkers and rate of cognitive decline in very mild dementia of the Alzheimer's type." Archives of Neurology 66(5): 638-645.

Sperling, R., S. Salloway, et al. (2012). "Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis." Lancet Neurol 11(3): 241-149.

Sperling, R. A., K. A. Johnson, et al. (2012). "Amyloid deposition detected with florbetapir F 18 ((18)F-AV-45) is related to lower episodic memory performance in clinically normal older individuals." Neurobiol Aging.

Strobel G. Aducanumab, Solanezumab, Gantenerumab data lift Crenezumab, as well. Series: Alzheimer's Association International Conference 2015, part 4 of 15. AlzForum [Internet].

2015. Available from: http://www.alzforum.org/news/conference-coverage/aducanumab-solanezumab-gantenerumab-data-lift-crenezumab-well.

Tarawneh, R., G. D'Angelo, et al. (2011). "Visinin-like protein-1: diagnostic and prognostic biomarker in Alzheimer disease." Ann Neurol 70(2): 274-285.

Varhaug K., Torkildsen Q, et al. (2019). "Neurofilament Light Chain as a Biomarker in Multiple Sclerosis." Front. Neurol 10:338

Walji, A. M., E. D. Hostetler, H. Selnick, Z. Zeng, P. Miller, I. Bennacef, C. Salinas, B. Connolly, L. Gantert and M. Holahan (2016). "Discovery of 6-(Fluoro-18 F)-3-(1 H-pyrrolo [2, 3-c] pyridin-1-yl) isoquinolin-5-amine ([18F]-MK-6240): A Positron Emission Tomography (PET) Imaging Agent for Quantification of Neurofibrillary Tangles (NFTs)." Journal of medicinal chemistry 59(10): 4778-4789

Wang, L., A. M. Fagan, et al. (2011). "Cerebrospinal Fluid Proteins Predict Longitudinal Hippocampal Degeneration in Early-stage Dementia of the Alzheimer Type." Alzheimer Dis Assoc Disord 26(4): 314-321.

Woodcock J, LaVange LM. (2017). "Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both." N Engl J Med 377:62-70.

APPENDIX 1: COGNITIVE RUN-IN PERIOD

DIAN-TU-001: A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive, and Clinical Endpoints in Dominantly Inherited Alzheimer's Disease

Regulatory Sponsor:	Washington University in St. Louis Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) Department of Neurology, Campus Box 8111, 660 S. Euclid Saint Louis, MO 63110
Study Product:	Not Applicable
Protocol Number:	DIAN-TU-001
Protocol Version:	Amendment 13
Version Date:	05 Apr 2023
IND Number:	115,652
EudraCT Number:	2013-000307-17

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1 INTRODUCTION

The purpose of the cognitive run-in (CRI) period is to establish a trial-ready cohort of participants for enrollment into study drug arms appended to this DIAN-TU-001 protocol, or drug arms to be opened under US NIH Grant U01 AG059798 (PI EM McDade) based on eligibility at the time a study drug arm is open for enrollment.

Run-in periods have several practical advantages, including increasing engagement of participants, establishing rapport with site personnel and personnel for home visits (if applicable), and familiarization of participants with the processes and procedures of the trial. One of the most important scientific advantages is a decrease in variability in cognitive test performance. A CRI period can reduce the effects of temporal fluctuations in performance by allowing participants to habituate to the testing process, thereby reducing practice effects, demand characteristics and test anxiety.

Moreover, results from clinical trials testing the β -secretase enzyme (BACE) inhibitors in those with and at risk for AD have identified evidence of an unanticipated cognitive decline. A CRI period offers the opportunity to more easily detect a deleterious drug effect by establishing a reliable baseline in participants where the majority of participants in the primary prevention population are cognitively normal at trial entry. This is particularly important for those participants that are much younger than their estimated age of onset where a decline in cognition would represent a significant deviation from the expected performance. This could be very helpful in identifying potential deleterious side effects of therapies at an earlier point and reacting appropriately.

The CRI period will help to ensure that a sufficient number of active and eligible participants qualify for entry into a study drug arm once opened to recruitment.

2 STUDY DESIGN FOR COGNITIVE RUN-IN PERIOD

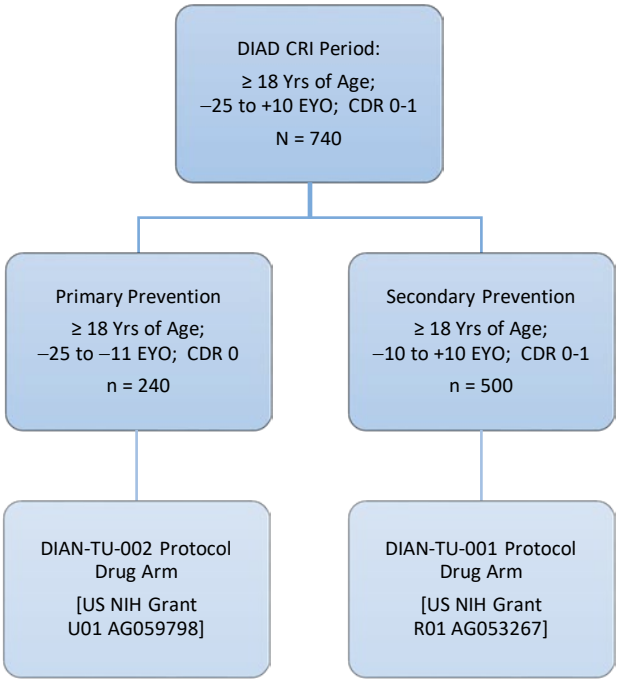
If no study drug arm is available for immediate enrollment or if a future drug arm is stopped prior to the planned completion (e.g., at biomarker interim, drug toxicity), a CRI period may be opened for recruitment by the sponsor. Participants considered for eligibility for the CRI period include participants 18 to 80 years of age who are either known to have a mutation causing Alzheimer's disease OR who do not know their gene status but are "at-risk" for a dominantly inherited Alzheimer's disease (DIAD) mutation AND who are either:

- cognitively normal or with mild cognitive impairment or mild dementia, Clinical Dementia Rating (CDR) 0 to 1 (inclusive) and within –10 to +10 years of the predicted or actual age at cognitive symptom onset (Secondary prevention population); target number of participants = 500
- cognitively normal and within 11 to 25 years younger (–25 to –11) than their estimated age at symptom onset (Primary prevention population); target number of participants = 240

The CRI period will consist of screening, entry, and follow-up visits and may last until a study drug arm opens for recruitment, but no longer than approximately 3 years.

Once a study drug arm is open for enrollment into the DIAN-TU-001 protocol, participants meeting the estimated years from symptom onset (EYO) entry criteria would be eligible for screening and a Screening visit (V1), conducted either in their home by a home health nurse or at the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) site, will be scheduled to collect safety labs and to reassess the suitability of the participant for entry into the trial (Section 6.3.2 of main protocol). A minimum of 8 weeks must elapse between the participant's last administration of a cognitive battery in the CRI period and administration of a drug arm's Baseline (V2) cognitive battery.

Figure 1 Cognitive Run-in Period Enrollment Scheme



Following approval of the DIAN-TU-002 (primary prevention) protocol in a given region, participants in the EYO range of primary prevention in this DIAN-TU-001 (secondary prevention) protocol may transition to the DIAN-TU-002 protocol. Data collected in both the DIAN-TU-001 and DIAN-TU-002 protocols will be shared.

3 STUDY PROCEDURES

3.1 Enrollment

See details in Sections 3.1 and 3.4 of the main protocol.

3.2 Specific Study Visits

3.2.1 CRI Screening Visit (CRI Screen)

The CRI screening period may last up to 8 weeks, starting at the collection of the first screening procedure (e.g., clinical safety lab collection). The participant is enrolled using the Interactive Web Response System (IWRS).

Location: CRI Screen procedures may be completed at a DIAN-TU qualified site or at the participant's home or other trial-identified location with the trial-certified cognitive rater/home health nurse. This visit also includes telephone calls with the DIAN-TU site staff. The participant may be contacted by their DIAN-TU site by telephone or during a regular DIAN Observational (DIAN-OBS) study visit. The participant is given the opportunity to review the informed consent form (ICF), ask questions and obtain answers, and sign the CRI ICF (only if the CRI period is enrolling).

Time/Timing: Informed consent must be obtained before any other study procedures. Informed consent, family history, demographic information and medical and treatment history may be obtained before the 2 to 8-week screening period begins. Informed consent should be obtained from both participant and study partner. Unless otherwise specified, all other CRI Screen procedures may occur throughout the screening period (2 to 8 weeks before CRI Entry). The CRI Screening visit in the home ensures participant eligibility before travel (if applicable) to the DIAN-TU site for CRI entry testing and enrollment.

Procedures (all can be performed by DIAN-TU site staff or trial-designated and trained home health nurse or other staff except as noted-see *Global Manual of Operations* and *DIAN-TU Cognition Core Procedures Manual* for additional details on order and timing of procedures):

- Obtain informed consent (DIAN-TU site staff must be available to answer questions)
- Enrollment in the IWRS
- Obtain or confirm family history and determine parental estimated age at onset and participant's actual age at onset, if symptomatic (DIAN-TU site staff). Estimated age at onset should be determined as outlined in the *Global Manual of Operations*.
- Verify documentation of participant's trial eligible mutation status ***OR*** confirm via family pedigree and mutation documentation (proband) that the participant is at risk for a trial-eligible mutation
- Collect demographic information and study partner information
- Obtain medical and treatment history, including assessment/recording of pre-existing conditions or adverse events
- Blood collection:
    - Genetic testing (results of genotyping of *APOE* and DIAD-associated genes (*APP*, *PSEN1*, and *PSEN2*) are not sent to the site to ensure genetic blinding is maintained)
    - Clinical laboratory tests, including hematology, chemistry, liver enzyme, TSH, B_{12}, hemoglobin A1c, PT, PTT, and INR

  - Serum pregnancy test for people of childbearing potential (POCBP); people who have undergone tubal ligations are also required to have pregnancy test performed.
- Urine collection for urinalysis
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight)
- Ambulatory Research in Cognition (ARC) smartphone-based cognitive assessment:
  - Set-up and training per Section 6.1.14.2 of main protocol
  - Participants will complete the first week of assessments immediately following the CRI Screen Visit (per Section 6.1.14.2 of the main protocol).

3.2.2 CRI Entry Visit (CRI Entry)

Location: Host DIAN-TU site

Time/Timing: Approximately a two (2) day visit that is scheduled 2 to 8 weeks after the CRI screening visit. The study partner participates in some of the procedures at CRI Entry and other annual visits at the DIAN-TU site. If possible, the study partner should accompany the participant to the DIAN-TU site for these visits. If this is not possible, the study partner procedures can be completed via telephone. The sequence and timing of visit procedures is very important. Detailed requirements and suggested timing of events at CRI Entry and at subsequent annual visits are detailed in the *Global Manual of Operations*. CRI Entry procedures may be scheduled over a longer time period of up to 2 weeks for participants living near the study site or if some study procedures (e.g., positron emission tomography [PET] scans) are done at a different DIAN-TU site.

The date of the cognitive battery test administered at the CRI Entry visit should be used to determine timing of subsequent visits for the CRI period.

Procedures:

- In-person review of informed consent for participants who provided consent over the telephone
- Medical/treatment history, including:
  - Concomitant medications
  - Assessment/recording of pre-existing conditions or adverse events
- Blood collection for provenance[7] testing of CRI Screening genetic sample (to confirm specimen identity)
- Urine pregnancy test for POCBP scheduled for [^{18}F]MK-6240 Tau PET
- Administration of the Columbia Suicide Severity Rating Scale (C-SSRS)
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, and height)

[7] Provenance testing is performed for quality assurance purposes to ensure that blood sample obtained at the CRI entry visit is from same individual as sample obtained at CRI screening visit.

- Blood collection (fasting) for plasma for biomarker analysis, stored plasma for future testing per Section 6.1.12. For participants having completed CRI Entry before approval of Amendment 13, this blood collection should be performed at the first opportunity, e.g. next site visit.
- Physical and neurological examinations
- Clinical assessments: CDR, calculation of Clinical Dementia Rating Sum of Boxes (CDR-SB), Geriatric Depression Scale (GDS), Functional Assessment Scale (FAS), Neuropsychiatric Inventory (NPI-Q) and Mini-Mental State Exam (MMSE), assessment of clinical diagnosis and clinician judgment of symptoms.
  Note*: For each participant, the CDR and assessment of clinical diagnosis should be administered by the same experienced clinician at all visits. Whenever possible, the CDR rater should not be involved in other clinical assessments (e.g., MMSE, FAS, GDS, NPI-Q) or in cognitive testing*.
- 12-lead electrocardiogram (ECG) (local)
- DIAN-TU Harmonized Cognitive Battery (per Section 6.1.14.2 of main protocol)
- Magnetic resonance imaging (MRI), including safety MRI sequences, to be performed on the first day
- [^{18}F]MK-6240 Tau PET scan (based on tracer availability and limited to participants –10 to +10 EYO [**NOT participants within –25 to –11 EYO at time of CRI Entry**])
- Final verification that all inclusion and no exclusion criteria are met (including receipt of MRI read)

3.2.3 CRI Visits 1, 3, 4, 6, 8, 10, and 12

Location: Visit will be conducted over the phone with the coordinator.

Time/Timing: Visits as listed below (calculated from day that the cognitive battery was completed at CRI Entry), with a visit window of ± 4 days.

Visit No.	1	3	4	6	8	10	12
Week	12	32	40	64	88	116	140

Procedures:

- Coordinator phone call to review any adverse events and concomitant medications

3.2.4 CRI Visits 2, 7, and 11

Location: DIAN-TU trial site or at the participant's home or other trial-identified location.

Time/Timing: Visits as listed below (calculated from day that the cognitive battery was completed at CRI Entry), with a visit window of ± 4 days.

Visit No.	2	7	11
Week	24	76	128

Procedures:

- Secondary Prevention Population:
  - Concomitant medications
  - Assessment/recording of adverse events
  - DIAN-TU Harmonized Cognitive Battery (per Section 6.1.14.2 of main protocol)
  - Clinical assessment: MMSE only
  - ARC smartphone-based cognitive assessments reminder for completion: participants will be prompted to begin the testing and will continue to complete the test over a continuous 7-day period. The test can be started within a ± 2-week window
  - Coordinator phone call to review any adverse events when the visit is conducted by a home health nurse
- Primary Prevention Population: Concomitant medications and adverse events will be assessed/recorded over the phone with the coordinator

3.2.5 CRI Visits 5, 9, and 13: ANNUAL VISIT AT HOST DIAN-TU SITE

Location: DIAN-TU site

Time/Timing: Visits as listed below (calculated from day that the cognitive battery was completed at CRI Entry), with a visit window of ± 7 days. Note that annual visits may take place over 2 or more days.

Visit No.	5	9	13
Week	52	104	156

Procedures:

- Concomitant medications
- Assessment/recording of adverse events
- Urine pregnancy test for POCBP scheduled for [^{18}F]MK-6240 tau PET
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature, weight, and height)
- Physical and neurological examination
- Clinical assessment: Full Battery: CDR, calculation of CDR-SB, NPI-Q, GDS, FAS, MMSE, and assessment of clinical diagnosis and clinician judgment of symptoms.
  NOTE*: For each participant, the CDR and assessment of clinical diagnosis should be administered by the same experienced clinician at all visits. Whenever possible, the CDR rater should not be involved in other clinical assessments (e.g., MMSE, FAS and GDS) or in cognitive testing.*

- DIAN-TU Harmonized Cognitive Battery (per Section 6.1.14.2 of main protocol)
- ARC smartphone-based cognitive assessments (reminder for completion): Participants will be prompted to begin the testing and will continue to complete the test over a continuous 7-day period.
- Secondary Prevention Population only:
    - MRI, including safety MRI sequences, to be performed for participants scheduled for [^{18}F]MK-6240 Tau PET Scan for V5 and V9.
    - [^{18}F]MK-6240 Tau PET Scan (based on tracer availability at time of CRI Entry) for V5 and V9. No Tau PET scan at V13.

4 ANALYSIS PLAN

The data collected during the CRI period will follow the participant when enrolled to a study drug arm.

The data from CRI primary prevention population will be used in the future drug arm in the primary prevention trial DIAN-TU-002.

5 ADVERSE EVENTS REPORTING

Adverse events will be reported as detailed in Section 7 of the main protocol.

REFERENCES

None.

SCHEDULE OF VISITS: Cognitive Run-In Period

Schedule of Visits: Cognitive Run-in Period – Screening through Week 104

Procedures	VISIT SITE[1,2]	Home (H)	DIAN-TU	Phone (Ph)	Ph/H	Ph	Ph	DIAN-TU	Ph	Ph/H	Ph	DIAN-TU
	Visit No.	Cognitive Run-in Screening Visit (CRI Screen)	Cognitive Run-in Entry Visit (CRI Entry)	CRI 1	CRI 2	CRI 3	CRI 4	CRI 5	CRI 6	CRI 7	CRI 8	CRI 9
	Timing (weeks)[3]	-8 to -2	0	12	24	32	40	52	64	76	88	104
Informed Consent[4]		X	X									
Enrollment in IWRS		X										
Verification of Inclusion/Exclusion Criteria			X									
Family History/Age at Onset Assessment[5]		X										
Demographics/Study Partner Information[5]		X										
Medical/Treatment History[6]		X	X									
Concomitant Medications			X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X[7]	X	X	X	X	X	X	X	X	X
Genetic Testing		X	X[8]									
Clinical Laboratory Tests: Hematology, Chemistry, Urinalysis[9]		X										
Pregnancy Testing[10]		X	X					X				X
C-SSRS			X									
Vital Signs[11]		X	X					X				X
Blood collection (fasting) for plasma biomarkers and stored plasma[19]			X[19]									
Physical/Neurological Exam			X					X				X
Clinical Assessment: Full Battery[12]			X					X				X
Secondary Prevention Population: Clinical Assessment: MMSE Only					X					X		
Local 12-Lead ECG[13]			X									
Primary Prevention Population: DIAN-TU Harmonized Cognitive Battery[14]			X					X				X

Schedule of Visits: Cognitive Run-in Period – Screening through Week 104

Procedures	VISIT SITE[1,2]	Home (H)	DIAN-TU	Phone (Ph)	Ph/H	Ph	Ph	DIAN-TU	Ph	Ph/H	Ph	DIAN-TU
	Visit No.	Cognitive Run-in Screening Visit (CRI Screen)	Cognitive Run-in Entry Visit (CRI Entry)	CRI 1	CRI 2	CRI 3	CRI 4	CRI 5	CRI 6	CRI 7	CRI 8	CRI 9
	Timing (weeks)[3]	-8 to -2	0	12	24	32	40	52	64	76	88	104
Secondary Prevention Population: DIAN-TU Harmonized Cognitive Battery[14]			X		X			X		X		X
Primary Prevention: ARC Smartphone-based Cognitive Assessments[15]		X						X				X
Secondary Prevention: ARC Smartphone-based Cognitive Assessments[15]		X			X			X		X		X
Volumetric MRI			X					X[16]				X[16]
Secondary Prevention: [^{18}F]MK-6240 Tau PET (when available)[17]			X					X				X
Coordinator Phone Call[18]					X					X		

Schedule of Visits: Cognitive Run-in Period – Week 116 through Week 156

Procedures	VISIT SITE[1,2]	Ph	Ph/H	Ph	DIAN-TU
	Visit No.	CRI 10	CRI 11	CRI 12	CRI 13
	Timing (weeks)[3]	116	128	140	156
Concomitant Medications		X	X	X	X
Adverse Event Assessment		X	X	X	X
Pregnancy Testing[10]					X
Vital Signs[11]					X
Physical/Neurological Exam					X
Clinical Assessment: Full Battery[12]					X
Secondary Prevention Population: Clinical Assessment: MMSE Only			X		
Primary Prevention Population: DIAN-TU Harmonized Cognitive Battery[14]					X
Secondary Prevention Population: DIAN-TU Harmonized Cognitive Battery[14]			X		X
Primary Prevention ARC Smartphone-based Cognitive Assessments[15]					X
Secondary Prevention ARC Smartphone-based Cognitive Assessments[15]			X		X
Coordinator Phone Call[18]			X		

Schedule of Visits: Cognitive Run-in Period - Footnotes

Footnotes:

1. Annual visits will be conducted at the host DIAN-TU site. For participants who live at a distance from the DIAN-TU site, other visits may be conducted at a site nearer to their home (H). See next two footnotes for additional detail.
2. Visits designated as occurring at home (H) may occur at the DIAN-TU site or, for participants who live at a distance from the DIAN-TU site, these visits may be conducted by a trial-designated home health nurse at the participant's home or other trial-identified location. These visits may include phone calls from the host DIAN-TU site staff.
3. The specific date of the cognitive battery administration at the Cognitive Run-In (CRI) Entry visit should be used to determine timing of subsequent visits.
4. The informed consent form (ICF) for CRI must be signed before any study procedures are performed.
5. Family history/age at onset and demographic information for participant and study partner will be collected during the CRI Screen visit and confirmed at the CRI Entry visit. This information will not be collected at subsequent visits unless the participant or study partner becomes aware of new information or the study partner changes during the study.
6. Home health nurses will have specific scripts or forms to prompt assessment and collection of medical treatment history, health changes or complaints (for assessment of adverse events by the site) and concomitant medications.
7. Preexisting conditions will be documented at CRI Screen visit and reviewed at CRI Entry visit.
8. Provenance testing to confirm specimen identity will be performed at CRI Entry visit only.
9. Clinical laboratory assessment scheduled for CRI Screen visit only; includes TSH, B_{12}, Hemoglobin A1c, PT, PTT, and INR.
10. Serum pregnancy testing will be performed at CRI Screening visit. Women who have undergone tubal ligations are also required to have pregnancy tests performed. Urine pregnancy test for people of childbearing potential who are scheduled for a [^{18}F]MK-6240 PET scan are to have a confirmed negative urine pregnancy test (HCG) on the day of PET imaging, before [^{18}F]MK-6240 dose administration. If PET scans are spread over more than one day, a urine pregnancy test should be completed either the day of or one day prior to any PET scan.
11. Vital signs include blood pressure, heart rate, respiratory rate, body temperature, and weight. Height collected at CRI Entry and annual visits only.
12. Clinical assessments at CRI Entry visit and annual visits. Study partner interview and administration of CDR and supplemental CDR-SB; clinician assessment of symptoms and diagnosis; Geriatric Depression Scale (GDS), Functional Assessment Scale (FAS), Neuropsychiatric Inventory (NPI-Q), and Mini Mental State Examination (MMSE).
13. Electrocardiogram (ECG) will be performed and read locally by a qualified physician or cardiologist. Investigators are to ensure no evidence of exclusionary findings.
14. Cognitive testing should be completed early in the day.
15. Ambulatory Research in Cognition (ARC) smartphone-based cognitive assessment, if applicable: participant will be prompted to begin the testing and will continue to complete the test over a continuous 7-day period. The test can be started with a ± 2-week window. See Section 6.1.14.2 of the main protocol and the DIAN-TU Cognition Core Procedures Manual for additional information.
16. Magnetic resonance imaging (MRI) required only for participants who are also scheduled for [^{18}F]MK-6240 Tau PET scan.
17. Sites with access to [^{18}F]MK-6240 tau tracer will participate including arranging for participants to scan at another DIAN-TU qualified site if not available at their enrolling site. Limited to participants who are −10 EYO to +10 EYO (not scheduled participants within –25 to –11 EYO at time of CRI Entry).
18. Site study coordinators should call participants either during or within two weeks after CRI 2, CRI 7 and CRI 11, if conducted via home health nurses. For primary prevention population, concomitant medications and adverse events will be assessed/recorded over the phone with the coordinator.
19. For participants having completed CRI Entry before approval of Amendment 13, this blood collection should be performed at the first opportunity, e.g., at the next site visit.

APPENDIX 2: MAIN PROTOCOL SCHEDULE OF VISITS: SCREENING AND BASELINE

PROCEDURES	VISIT SITE	Home (H)[1]	DIAN-TU
	Visit No	V1 (screen)	V2 (baseline)
	Timing (weeks)[2]	–8 to –2	0
Informed Consent[3]		X	X[4]
Family History/Age at Onset Assessment[5]		X	
Demographics/Study Partner Information[5]		X	
Medical/Treatment History[6]		X	X
Concomitant Medications			X
Adverse Event Assessment		X	X[7]
Genetic Testing/*APOE*[8]		X	X[9]
Hematology, Chemistry, Urinalysis [10]		X	
Pregnancy Testing[11]		X	X
Drug-specific Labs			X[12, 13]
Stored Plasma and/or Serum and DNA[14]			X
C-SSRS		X	X
Vital Signs[15]		X	X
Physical/Neurological Exam			X
Clinical Assessment[16]			X
12-Lead ECG			X
DIAN-TU Harmonized Cognitive Battery[17]		X	X
ARC Smartphone-based Cognitive Assessments[21]		X	X[22]
Annual/Volumetric MRI			X
Lumbar Puncture (CSF)[18]			X
PET Imaging			X[19]
3T Safety and Volumetric MRI			X
Randomization			X[20]
Study Drug Administration			X

Footnotes:

1. Visits (designated as occurring at home[H]) may occur at the DIAN-TU site or, for participants who live at a distance from the DIAN-TU site, these visits may be conducted by a home health nurse at the participant's home or other trial-identified location. These visits may include phone calls from the host DIAN-TU site staff.
2. The specific date during the baseline visit (V2) when the first dose of study drug is administered should be used to determine timing of subsequent visits and for calculating time between screening visit (V1) and baseline visit (V2).
3. Informed consent may be obtained in two steps if more than one drug is enrolling concurrently. Participants will have the opportunity to review the main informed consent form (ICF) and, if applicable, the supplemental drug-specific ICF and to discuss with DIAN-TU site study staff on the phone or in-person. They can sign the main ICF at home or at the DIAN-TU site. The main ICF must be signed before any study procedures are performed. After screening labs are obtained and the participant is randomized to a specific study drug arm at V2, the participant will review and sign a supplemental study drug-specific consent that details specific risks/benefits and procedures for the study drug arm to which they were assigned, when applicable. If only one study drug arm is enrolling, one consent may be used in the same fashion as the 'main consent' is referenced within.

4. If applicable, study drug-specific supplemental consent should be reviewed and signed after randomization.
5. Family history/age at onset and demographic information for participant and study partner will be collected during the screening period and confirmed at the baseline visit, if not already collected during the Cognitive Run-In (CRI) period. This information will not be collected at subsequent visits unless the participant or study partner becomes aware of new information or the study partner changes during the study.
6. Home health nurses (HHNs) will have specific scripts or forms to prompt assessment and collection of medical treatment history, health changes or complaints (for assessment of adverse events by the site) and concomitant medications. Results from CRI period may be used unless the participant or study partner becomes aware of new information.
7. Preexisting conditions will be documented at screening visit and reviewed at baseline visit (V2) prior to study drug administration.
8. Genetic testing does not need to be repeated if results from the CRI period are available.
9. Provenance testing to confirm specimen identity will be performed at baseline visit only (V2), if not completed at the CRI Entry visit
10. Includes TSH, B_{12}, hemoglobin A1c, PT, PTT, and INR are collected at Visit 1 only
11. Serum pregnancy testing will be performed at screening (V1) and safety follow-up visit. Urine pregnancy testing will be performed at V2. Pregnancy tests must be confirmed as negative prior to dosing with study drug. Urine pregnancy test must be completed and confirmed as negative either the day of or the day prior to any PET scan; if PET scans occur on more than 2 consecutive days during annual visits more than one urine pregnancy test will be required. Women who have undergone tubal ligation are required to have pregnancy tests performed. Alternate tests may be used if urine collection is not feasible but must be approved by the sponsor in advance.
12. Pharmacokinetic (PK) blood samples will be obtained before study drug administration. Time of collection and timing of drug administration will be recorded.
13. See each drug-specific appendix for additional details.
14. For future studies, including future regulatory inquiries or additional monitoring of anti-drug antibodies or other drug-specific tests. See main protocol Section 6.1.12.
15. Blood pressure, heart rate, respiratory rate, and body temperature will be collected at all visits. Height and weight will be measured at baseline (V2).
16. Clinical assessments: DIAN-TU clinical assessment battery includes: study partner interview and administration of Clinical Dementia Rating (CDR) and supplemental CDR-SB; clinician assessment of symptoms and diagnosis; Geriatric Depression Scale (GDS), Functional Assessment Scale (FAS), Neuropsychiatric Inventory (NPI-Q), and Mini Mental State Evaluation (MMSE).
17. The DIAN-TU Harmonized Cognitive Battery will be administered by a trial-certified cognitive rater. See Section 6.1.14.2 of the main protocol and the arm-specific *DIAN-TU Cognition Core Procedures Manual* for additional information. Cognitive testing should be completed before study drug infusion or injection.
18. Lumbar puncture (LP) should be performed after magnetic resonance imaging (MRI), if on the same date. Lumbar punctures should be performed at approximately 8 am local time under fasting conditions (water is allowed and encouraged). Cerebrospinal fluid (CSF) will be sent to a local laboratory for cell count and differential, glucose and protein as well as to central lab for sample management, including Washington University Biomarker Core lab and designated research/referral labs for biomarker and drug-specific analyses. Site staff should contact the participant 24-48 hours after the LP to assess for adverse effects of the LP.
19. See details in each drug-specific appendix.
20. Prior to randomization, verify that all inclusion/exclusion criteria are met, including ARIA findings on baseline MRI.
21. Ambulatory Research in Cognition (ARC) smartphone-based cognitive assessment: participant will be prompted to begin the testing and will continue to complete the test over a continuous 7-day period. The test can be started with a ± 1-week window. See Section 6.1.14.2 of the main protocol and the DIAN-TU Cognition Core Procedures Manual for additional information.
22. Participants who are CDR=1 at Baseline (V2) will not be expected to continue ARC assessments and will be asked to uninstall the application.

APPENDIX 3: GANTENERUMAB

DRUG-SPECIFIC INFORMATION:

Gantenerumab (RO4909832)

DIAN-TU-001: A Phase II/III Multicenter Randomized, Double-Blind, Placebo-Controlled, Platform Trial of Potential Disease Modifying Therapies Utilizing Biomarker, Cognitive and Clinical Endpoints in Dominantly Inherited Alzheimer's Disease

Regulatory Sponsor:	Washington University in St. Louis Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) Department of Neurology Campus Box 8111, 660 S. Euclid Saint Louis, MO 63110
Study Product:	Gantenerumab (RO4909832)
Protocol Number:	DIAN-TU-001
Protocol Version:	Amendment 13
Version Date:	05 Apr 2023
IND Number:	115,652
EudraCT Number:	2013-000307-17

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1 DRUG-SPECIFIC INTRODUCTION

1.1 Background

Both active and passive immunization strategies directed against amyloid beta peptides are currently under investigation. The first preclinical studies demonstrating reduction in amyloid burden were performed in APP^{V717F} ("PDAPP") transgenic mice over 22 years ago (Schenk et al., 1999; Bard et al., 2000). The PDAPP mouse and all other genetic mouse models of AD are based on the mutations in *APP*, *PSEN1* and *PSEN2* that underlie the dominantly inherited forms of AD represented in the DIAN cohort. The preclinical studies in these mouse models are highly relevant to these individuals than to those with sporadic AD.

1.2 Study Drug

Gantenerumab is a fully human IgG1 antibody which binds specifically to aggregated forms of Aβ (including oligomers, fibrils, and plaques) and targets the amyloid pathology associated with AD.

1.3 Preclinical Data

Gantenerumab is a recombinant, completely human, monoclonal antibody of the IgG1 subclass directed against the Aβ peptide. It is a novel type of antibody that recognizes a conformational epitope of Aβ and binds to both major types of Aβ ($Aβ_{40/42}$). Binding characteristics for gantenerumab were engineered to achieve specific and highly sensitive recognition of aggregated Aβ, like the fibrillar assembly structure of the human Aβ peptide, which is the predominant component in Aβ plaques. Gantenerumab recognizes aggregated Aβ with high affinity (Kd ~ 0.5 nM) as determined in vitro. Specificity was demonstrated for native human Aβ plaques on brain sections. The minimal effective concentration for staining of human Aβ plaques was determined to be 10 ng/mL (0.07 nM).

In functional assays gantenerumab induced cellular phagocytosis of human Aβ deposits in AD brain slices when co-cultured with primary human macrophages and neutralized oligomeric $Aβ_{42}$-mediated inhibitory effects on long-term potentiation in rat brain. In APP751swedishxPS2N141I transgenic mice, gantenerumab showed sustained binding to cerebral Aβ and, upon chronic treatment, significantly reduced small Aβ plaques by recruiting microglia and prevented new plaque formation. Unlike other Aβ antibodies, gantenerumab did not alter plasma Aβ suggesting undisturbed systemic clearance of soluble Aβ. Overall, gantenerumab preferentially interacts with aggregated Aβ in the brain and lowers Aβ by eliciting effector cell-mediated clearance (Bohrmann et al., 2012; Ostrowitzki et al., 2012).

Effective brain penetration and binding to Aβ plaques was demonstrated in a double-transgene mouse model expressing AD-related mutations that display a pronounced amyloidosis phenotype. Gantenerumab showed significant Aβ plaque binding up to nine weeks, indicating

that there is no requirement for continuous high peripheral levels to achieve a sustained binding of gantenerumab to amyloid plaques.

1.4 Clinical Data

A summary of the available results of completed clinical studies with gantenerumab is presented in this section. For a more thorough description, refer to the IB.

BN18726

A total of 30 patients (16 males, 14 females) diagnosed with mild to moderate probable AD participated in a single ascending dose (SAD) study (BN18726) which was completed in August 2008. Patients received a single IV (intravenous) dose of gantenerumab (doses ranging from 6 mg to 400 mg) or placebo. All patients completed the SAD study and gantenerumab was well tolerated.

WP22461

WP22461 was a bioavailability study conducted in 42 healthy male participants. The study evaluated safety, tolerability, and pharmacokinetics (PK) of gantenerumab following a single IV infusion or subcutaneous (SC) injection. In this study, participants received a single dose of gantenerumab at the following doses and routes: 60 mg by IV infusion, 75 mg SC injection, or 150 mg SC injection. Gantenerumab was generally well tolerated when administered SC.

JP22474

Study JP22474 was a Phase I SAD study designed to investigate safety, tolerability, PK and PD after IV infusion of gantenerumab in Japanese AD patients. The results showed that single IV doses of up to 200 mg gantenerumab were well tolerated.

NN19866

In the multiple ascending dose (MAD) study (NN19866), a total of 60 patients (34 males and 26 females) diagnosed with mild to moderate probable AD received multiple IV doses of gantenerumab (doses of 6 mg, 20 mg, 60 mg, and 200 mg) or placebo on an every 4-week (Q4W) schedule for up to 7 months. Due to findings of “vasogenic edema” and “microbleeds” on brain magnetic resonance imaging (MRI) scans (amyloid-related imaging abnormalities or ARIA) which occurred in some patients in cohort 4 (gantenerumab 200 mg or placebo), it was decided to terminate dosing for all patients on June 9, 2008. At that time, 16 patients were receiving 200 mg of gantenerumab, and 4 patients were receiving placebo. These patients had received between 2 to 5 doses each. When the patients were then genotyped for *APOE*, *APOE4* carrier status emerged as a risk factor for the occurrence of these MRI findings, as has been reported for bapineuzumab. The MRI findings are described further below. Otherwise, gantenerumab was well tolerated in NN19866.

NN19866 Pharmacodynamics

In a substudy of NN19866 (NN19866-PET), the protocol was amended in order to evaluate the effect of gantenerumab on amyloid load in the brain (defined as standardized uptake value ratio of a cortical composite volume of interest over cerebellar cortex and using [^{11}C]PiB-PET) in 18 patients (4 in the placebo group, 8 in the 60-mg dose group and 6 in the 200-mg dose group). A median decrease from baseline [redacted] was seen in the gantenerumab 200 mg dose group while an increase was seen in the placebo group [redacted] and relative stability compared to baseline in the 60-mg group [redacted]

NN19866 Magnetic Resonance Imaging

The multiple ascending dose (MAD) study NN19866 was prematurely terminated (after patients in the 200-mg group had received 2 to 5 doses) due to ARIA-E seen after 2 to 4 doses of gantenerumab 200 mg. Notably, the findings, best seen on the Fluid Attenuated Inversion Recovery (FLAIR) sequences, were only reported in carriers of *APOE-4* and seemed more prominent in patients who were homozygous for *APOE-4* (E4/E4). Concomitant ARIA-H microbleeds were only observed in the two carrier patients homozygous for *APOE4* (E4/E4). No patient required treatment and the ARIA-E findings spontaneously resolved 1 to 4 months after discontinuation of gantenerumab.

JP22431

In a MAD study (JP22431), a total of 29 patients diagnosed with mild to moderate probable AD received multiple SC doses of gantenerumab (doses of 75 mg, 105 mg, and 225 mg) or placebo on Q4W schedule for up to 7 months. Gantenerumab was generally well tolerated when administered SC.

WP27951

A study comparing lyophilized (Lyo-F) and high-concentration liquid formulations (HCLF) included a total of 120 healthy participants. Participants were randomized to receive single SC doses of either 105 or 225 mg of the Lyo-F formulation or 105, 225, or 300 mg of the HCLF formulation. Gantenerumab was generally well tolerated when administered SC.

BP29113

A study comparing Lyo-F and HCLF formulations included a total of 48 healthy participants. Participants were randomized to receive single SC dose of 225 mg in a pre-filled syringe or as a lyophilized formulation. Gantenerumab was generally well tolerated when administered SC.

BP30042

A study assessing the safety and tolerability of single ascending doses of SC gantenerumab included a total of 38 healthy male participants (32 on gantenerumab and 6 on placebo). Participants were randomized to receive single doses of 450 mg, 900 mg or 1500 mg.

Gantenerumab was generally well tolerated up to the highest tested dose when administered SC.

WP39322

A study comparing pain of a single dose of gantenerumab administered SC in the abdomen included a total of 50 participants. Participants were randomized to receive a single dose of 300 mg in the abdomen in 5 or 15 seconds followed by 2 SC administrations of a placebo solution (one in abdomen and one in the thigh). Gantenerumab was generally well tolerated.

WP40052

A study comparing the relative bioavailability, safety and tolerability following single dose SC administration of 600 mg of gantenerumab produced with the G3 (Reference) or G4 (Test) process included a total of 114 healthy participants. The plasma exposure in terms of area under the concentration-time curve between time 0 and time infinity (AUC_{Inf}) was approximately 1.18-fold higher after SC administration of 600 mg gantenerumab G4 compared to 600 mg gantenerumab G3, whereas maximum plasma concentrations (C_{max}) were similar. Gantenerumab produced with either process was generally well tolerated.

Clinical Pharmacokinetics (PK)

The PK of gantenerumab after intravenous administration were investigated in White patients with mild to moderate AD after single (Study BN18726) and multiple doses (Study NN19866), after single dose in Japanese patients with mild to moderate AD (Study JP22474), and after single dose in healthy volunteers (Study WP22461).

CCI [redacted] lasma concentrations of gantenerumab appeared to increase dose-proportionally after intravenous dosing.

CCI [redacted] CCI

The PK of gantenerumab following a single SC dose was assessed in 6 studies in healthy volunteers (WP22461, WP27951, BP29113, BP30042, WP39322 and WP40052).

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

In general, gantenerumab exposures increased dose proportionally. CCI [redacted]

Phase III Studies

Global Phase III studies investigating the effect of SC gantenerumab on cognition and function initially included Study WN25203 in participants with prodromal AD, and Study WN28745 in participants with mild AD, subsequently converted to open-label extensions; and later two multicenter, double-blind, randomized, placebo-controlled Phase III studies, WN29922 (Graduate 1) and WN39658 (Graduate 2), in patients with early (prodromal to mild) AD.

Further details from each study are summarized below.

WN25203

WN25203 was a Phase III study investigating the effect of SC gantenerumab on cognition and function in prodromal AD with futility analysis conducted when 50% of the participants completed treatments for 2 years. The doses in the study were 105 mg and 225 mg SC every 4 weeks for 4 years (including a 2-year double-blind placebo-controlled extension). Because ARIA findings seemed to be more frequent in carriers of *APOE ε4* in the earlier MAD study, participants who were homozygous for this gene initially did not receive the dose of 225 mg SC in Study WN25203, but an amendment later allowed for full dose regardless of *APOE ε4*. This futility analysis took place in December 2014 and led to the study being declared futile and

suspension of dosing. No safety issues were identified in the futility analysis. Subsequently, the trial has continued as an open-label extension utilizing doses of up to 1200 mg Q4W.

WN25203-PET

Study WN25203 included a substudy, WN25203-PET, designed to assess changes in amyloid load over time in a subset of patients with prodromal AD by PET imaging using the amyloid tracer Florbetapir 18F (18F-AV-45; AMYViD). Results from amyloid PET assessments show clear dose- and time-dependent reductions in cortical to cerebellum standard uptake value ratios (SUVr), with greater reduction over longer periods of exposure to gantenerumab. This reduction was present regardless of the reference region utilized for the analysis. Patients in the 225 mg gantenerumab arm showed consistent and potentially cumulative SUVr reduction of 5 to 10% over a period of 2 to 3 years. In an analysis of the concentration dependence of the SUVr reductions, patients with greater concentrations of gantenerumab experienced greater reductions in SUVr.

WN28745

Study WN28745 was initially designed as a 2-year, double-blind, placebo-controlled, efficacy and safety study of gantenerumab in approximately 1000 patients with mild AD, and was initiated in the first quarter of 2014. Patients with probable mild AD were identified based on established NINCDS/ADRDA clinical criteria, low CSF $A\beta_{42}$, and cognitive decline. The co-primary efficacy endpoints included measures of cognition (Alzheimer's Disease Assessment Scale - Cognitive Subscale [ADAS-Cog]) and function (Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory [ADCS-ADL]). Based on the initial design of WN28745, all patients were to follow a slow titration scheme independent of the *ApoE* ε4 genotype, starting gantenerumab at 105 mg SC Q4W (every 4 weeks) for seven doses, with progression to 225 mg, based on acceptable MRI findings. The study enrolled 389 patients. Analysis of the WN25203 results, and data from other AD studies, indicated that efficacy would likely be apparent at much higher doses than originally tested in the Phase III Studies. As a result, enrollment in the double-blind phase of the WN28745 study was halted in November 2015. The study was amended into an open-label extension evaluating the safety and tolerability of gantenerumab at higher doses (up to 1200 mg) using different titration schemes. In Study WN28745, gantenerumab, at a dose of 105 mg SC Q4W for 6 months followed by 225 mg SC Q4W for up to 24 months, was safe and well tolerated by patients with mild AD.

Dosing of Gantenerumab up to 1200 mg Q4W: Open-label Extensions of WN25203 and Study WN28745; and Placebo-controlled Period of DIAN-TU-001 Study

Both protocols for Studies WN25203 and WN28745 were amended to convert the studies into open-label extensions to evaluate SC dosing of gantenerumab up to target dose of 1200 mg Q4W. Overall 154 of the 799 patients originally randomized into the study entered the WN25203 OLE. Overall, 230 of 389 patients originally randomized into the study entered the WN28745 OLE.

Eighty-nine patients were initially enrolled in the OLE PET substudies, of whom 67 patients received follow-up scans at OLE week 52, 40 received scans at OLE week 104, and 23 received scans at OLE week 156 by the cutoff date of 31 May 2019. Patients were divided into three analysis cohorts due to heterogeneous baseline characteristics, time off-dose before OLE dosing, and OLE titration schedules: 1) MR-DBP: patients in the placebo arm of WN28745 Marguerite RoAD, 2) MR-DBA: patients in the active treatment arms of WN28745, and 3) SR: a combined cohort of all patients from the WN25203 Scarlet RoAD study. SR patients were combined into a single cohort since all patients were off dose for 16 to 19 months prior to OLE dosing. CCI [redacted] Amyloid reductions are consistently seen in nearly all patients of the three analyzed subgroups.

The study showed higher reductions of amyloid plaque over a shorter time period with the 1200 mg dosing regimen of gantenerumab compared to 105 or 225 mg dosing. CCI [redacted]

Study WN25203 included a substudy, WN25203-PET, designed to assess changes in amyloid load over time in a subset of patients with prodromal AD by PET imaging using the amyloid tracer Florbetapir 18F (18F-AV-45; AMYViD). Results from amyloid PET assessments showed clear dose- and time-dependent reductions in cortical to cerebellum standard uptake value ratios (SUVr), with greater reduction over longer periods of exposure to gantenerumab. This reduction was present regardless of the reference region utilized for the analysis. Patients in the 225 mg gantenerumab arm showed consistent and potentially cumulative SUVr reduction of 5 to 10% over a period of 2 to 3 years. In an analysis of the concentration dependence of the SUVr reductions, patients with greater concentrations of gantenerumab experienced greater reductions in SUVr.

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In the WN28745-Tau PET substudy, there was no temporal association between the tau tracer administration and AEs.

In the OLE phase of Studies WN25203 and WN28745, gantenerumab, in doses of up to 1200 mg SC Q4W for up to 236 weeks (~4.5 years) for WN25203, and 245 weeks (~4.5 years) for WN28745, was safe and well tolerated by patients with AD.

In the DIAN-TU-001 study, there was no benefit of gantenerumab observed on the primary endpoint, the DIAN Multivariate Cognitive Endpoint (DIAN-MCE), or on clinical endpoints Clinical Dementia Rating Sum of Boxes (CDR-SB) and Functional Assessment Scale (FAS). However, potential cognitive impact was inconclusive given that the asymptomatic placebo group showed no cognitive decline, and symptomatic patients had declined substantially before reaching target doses. Gantenerumab significantly reduced brain Aβ deposition, cerebrospinal fluid (CSF) total tau, and CSF pT181, and attenuated the increase of neurofilament light chain

(NfL). Aβ Pittsburgh compound B positron emission tomography (PiB-PET) results demonstrated significant reduction of Aβ deposition with gantenerumab compared to placebo at years 2 and 4. Gantenerumab was safe and well tolerated in doses up to 1200 mg SC Q4W (G3). During the placebo-controlled period of the trial, amyloid-related imaging abnormalities-cerebral edema (ARIA-E) were observed in 19.2% (10/48) of the gantenerumab group; compared to the placebo group, participants in the gantenerumab arm were more likely to develop ARIA-E (odds ratio [OR]=9.29, 95% confidence interval [CI]=[1.1, 75.9], p<0.05). ARIA-E cases were PiB+ and 60% had cognitive impairment (CDR>0). ARIA-E cases were mostly asymptomatic for lesion associated neurologic change (8/10); if symptoms occurred (2/10), they were mild in nature and resolved. ARIA-E events were managed by temporarily withholding the dose and resuming at similar or lower doses, with most reaching the target dose (3/10 ARIA-E cases discontinued from the trial, mainly to AD progression). *APOE* genotype was predictor of ARIA-E. ARIA-E frequency was 31% in *APOE*-ε4+ and 14% in *APOE*-ε4- (OR=5.0, 95%; CI [1.0, 30.4], p=0.055). Seventy (70) percent of the ARIA-E cases occurred at higher doses (900 mg or more) and generally after 2 doses of a titration dose. However, the mean severity as measured by Barkhof score was similar regardless of the dose (higher dose=2.8 vs lower doses=3.5).

ARIA-E findings were clinically manageable by protocol-defined MRI monitoring and dose intervention algorithms. Clinical symptoms were experienced by a minority of patients with ARIA findings on MRI. If clinical symptoms did occur, they tended to be mild and non-serious, and resolved upon dosing suspension. All serious symptoms that have occurred in patients with ARIA-E (4 cases of seizure/epilepsy, 2 cases of stroke-like symptoms, and 1 case of serious confusion) resolved following the protocol-mandated dosing intervention and ARIA resolution.

Immunogenicity and Safety

CCI [redacted] Beyond ARIA events, injection site reactions were the most common event occurring more frequently with gantenerumab than with placebo; these events were also mild, non-serious, in WN25203 double-blind period CCI [redacted] CCI [redacted] No drug-effect on white blood cells or neutrophils was observed.

The identified risks of gantenerumab treatment are ARIA of edema/effusion (ARIA-E) and of microhemorrhage/hemosiderin deposition (ARIA-H), and injection-site reactions (ISRs) associated with SC administration.

WN29922 and WN39658

Summary

Early evidence with anti-amyloid monoclonal antibodies revealed dose-dependent ARIA, and effects on clinical and cognitive outcomes with significant amyloid plaque removal (Mintun et al., 2021; Swanson et al., 2021). Evidence from two clinical trials with similar antibodies against aggregated Aβ including plaques (i.e., gantenerumab and aducanumab) provide new insights into the biological mechanism of aggregated amyloid removal.

This evidence also indicates that ARIAs are predictable and manageable events. Gantenerumab data also suggest that beneficial effects on target and downstream biomarkers effects are measurable and reproducible (gantenerumab WN25203 positron emission tomography [PET] and cerebrospinal fluid [CSF] data).

ARIAs and injection site reactions are the safety risks that have emerged to date for gantenerumab. Overall, gantenerumab up-titration has been implemented with the objective to reduce the risk of ARIA-E; ARIA-E incidence observed in the open-label extensions has been in the expected range and in alignment with the ARIA-E PK-PD model. ARIAs are clinically manageable by protocol-defined MRI monitoring and dose intervention algorithms.

A dedicated risk management for ARIA has been implemented. It appears that appropriate MRI monitoring associated with drop-out criteria provides a sufficient risk minimization.

No other clinical safety liabilities of major relevance have emerged.

1.5 Dose Selection/Rationale

1.5.1 Double-Blind Period (1200 mg Q4W, G2 and G3 Formulations)

The initial dose in the DIAN-TU-001 study double-blind period was 225 mg gantenerumab, administered subcutaneously (SC), every 4 weeks (Q4W). The study was initiated using the lyophilized formulation (generation 2 [G2]) and transitioned to the high concentration liquid formulation ([HCLF], generation 3 [G3]) as detailed below.

This dosing regimen was investigated in heterozygous carriers and non-carriers of *APOE4* in the WN25203 (Scarlet RoAD) trial with an acceptable safety profile. In WN25203, the dose administered to homozygous *APOE4* carriers was 105 mg Q4W SC.

The starting dose of 225 mg of the G2 formulation in the DIAN-TU-001 study, including participants homozygous for the *APOE4* allele was justified based on the following considerations:

- The DIAN-TU-001 study applied similar MRI monitoring scheme to WN25203 and WN28745 with a predefined ARIA related intervention algorithm
- All new ARIA findings were reviewed by the Project Arm Leader (PAL), Medical Director or designee who advised the site on whether a more conservative approach should be considered than defined in the ARIA related intervention algorithm (Section 1.14)
- Participants recruited into the trial were generally at an early stage of the disease, i.e., at an earlier clinical stage or a similar stage as requested for prodromal and mild (sporadic) AD patients in the ongoing WN25203 and WN28745 trials
- The dominantly inherited mutation carrier status (rather than *APOE* genotype) was the predominant risk for AD and for amyloid deposition in the DIAN-TU population
- Given the PET data obtained in the MAD study (Study NN19866) where decreases in the amyloid plaque burden were observed, the dosage selected based on systemic overall exposure was expected to reduce the plaque burden relative to placebo

Based on results of a pre-planned futility analyses in the concurrent gantenerumab study (WN25203) and similar monoclonal antibody (aducanumab) data emerging at much higher doses in sporadic Alzheimer's disease following approval of Amendment 5, all participants initiated up–titration which included transition to the HCLF G3 formulation. CCI [redacted]

1.5.2 Open-Label Extension (1500 mg Q2W, G4 Formulation)

1.5.2.1 Dose Regimen

The initial target dose in the OLE period was CCI [redacted] Unless otherwise stated, gantenerumab product used within the OLE study period refers to the G4 formulation.

The dose will be slowly increased via multiple titration steps similar to that used in the double-blind period of the trial. Participants will follow the previously established OLE titration schedule to reach CCI by receiving CCI doses at each titration step; CCI CCI CCI and then CCI . After CCI doses at CCI , the dosing frequency will increase to CCI and participants will receive CCI for 12 weeks, and then the final, target dose of CCI thereafter (Figure 1). The entire dose titration period will take 15 months. At some sites, participants may have received 3 or more doses at CCI before regulatory approval and consenting to Amendment 11 is completed. Those participants will proceed to initiate titration beyond CCI as soon as approvals are in place.

For the study drug administration visits following the occurrence of a safety MRI, the site principal investigator or designated sub-investigator must review the MRI central read prior to proceeding with the subsequent dose administration.

1.5.2.2 PK/PD (Amyloid PET) Model-Based Dose Selection

Comparison of PET data from DIAD and sporadic AD (sAD) studies indicated that DIAD participants with mutations have higher amyloid growth rates and lower amyloid plaque removal following administration of gantenerumab than participants in sAD studies who received a similar gantenerumab regimen. Extensive analyses were performed of the double-blind period data and a combined sAD–DIAD PK/PET model of gantenerumab was developed to assess the effect of gantenerumab on amyloid plaque removal (PK/PD Model). The quantitative results suggest that an approximate 3-fold higher dose of gantenerumab is required in DIAD mutation carriers compared to sAD to bring most participants below the amyloid threshold of positivity (20 centiloids) within 2 years and to fully remove amyloid plaques within 3-4 years. As greater amyloid removal is anticipated to increase the likelihood of subsequent improvement in cognitive and clinical response, this dose increase was considered necessary in the DIAD population. CCI [redacted] double-blind period of the DIAN-TU-001 trial as a higher dose significantly

reduced CSF total tau and phospho tau 181 (ptau181), and significantly slowed increases in CSF NfL.

1.5.2.3 Safety Monitoring

During the double-blind period of the DIAN-TU-001 trial, which used the same target gantenerumab dose as in the sporadic AD trials (Studies WN29922 and WN39658), the safety profile of gantenerumab was consistent with trials in sporadic AD. In DIAN-TU-001, amyloid-related imaging abnormalities-edema (ARIA-E) were observed in 19.2% (10/52) of the gantenerumab group. Most ARIA-E occurred at doses over 900 mg Q4W. ARIA-E cases were mostly asymptomatic (7/10); if symptoms occurred (3/10), they were mild in nature and resolved. Mean severity score measured by Barkhof score was similar regardless of the dose (Higher dose=2.8 vs Lower doses=3.5). *APOE* genotype was a predictor (OR=5.0, 95%CI=1.0-30.4) of ARIA-E during the double-blind period with 6 out of 10 ARIA-E cases being *APOE-ε4* carriers.

MRI Monitoring and Sentinel Cohort

This titration schedule in the DIAN-TU-001 OLE period will allow for a slow dose escalation over a minimum of 15 months with frequent safety MRI scans to monitor and respond to radiographic ARIA (Figure 1). In addition to the titration safety MRI and stable dose MRI schedules in Figure 1 and Table 5, participants will be regularly monitored for health changes or complaints.

Further outlined is the planned inclusion of a sentinel cohort for additional MRI monitoring in DIAN-TU-001 OLE. The first 20 participants receiving two doses of 1020 mg Q2W will receive an additional safety MRI scan and safety clearance before proceeding with further participant exposure to this dose level. In similar fashion, the first 20 participants receiving two doses of 1500 mg Q2W will receive an additional MRI with safety clearance before proceeding with further participant exposure to this dose level. No further participants will be eligible to up-titrate to the 1020 mg Q2W and 1500 mg Q2W dose levels until a safety review of the respective sentinel cohort has been completed.

The DIAN-TU Medical Monitors will review individual MRI changes and ARIA cases following the ARIA-Related Interventions outlined in Section 1.14 in addition to quarterly aggregate safety data reviews.

Data Safety Monitoring Board (DSMB)

At a study-wide level, dosing and safety will be monitored by an experienced DSMB with participant-matter experts on ARIA, amyloid removal, and AD to inform about the target dose for OLE. DSMB monitoring will occur on a quarterly basis and will include review of ARIA cases, in addition to the sentinel cohort data.

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1.6 Risks/Benefits

Participants in this study who receive active study drug have dominantly inherited Alzheimer's disease (DIAD) mutations in presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*) and amyloid precursor protein (*APP*) with very high penetrance (near 100%). AD is a progressive and ultimately fatal disease, and no disease-modifying treatment is available to date.

Plaque removal effect was demonstrated in the prodromal AD study WN25203 with the higher 225 mg dose showing a stronger effect of removal. These results for the first time showed the effect of immunotherapies against Aβ in early (prodromal) AD. In DIAD, amyloid deposition is present at early asymptomatic stages of the disease when no memory impairment is present (Bateman et al., 2012). In the DIAN-TU-001 study, gantenerumab reduced amyloid plaques in a dose-dependent fashion during the double-blind phase, however the 1200 mg Q4W dose did not fully remove amyloid plaques as measured by PiB-PET. Given that prior imaging and neuropathological work suggest that pathology accumulates 3-fold faster and to a greater extent in DIAD than sporadic AD (Shepherd et al., 2009; Ringman et al, 2016), higher dose and longer duration of treatment may be needed to reduce amyloid to an amyloid negative level in the DIAD population. Therefore, during the OLE period we will increase the dose of gantenerumab CCI to CCI

The quantitative results suggest that an approximate 3-fold higher dose of gantenerumab is required in DIAD mutation carriers compared to sAD to bring the majority of participants below the amyloid threshold of positivity (20 centiloids) within 2 years and to fully remove amyloid plaques within 3-4 years (Section 1.5.2.2). The amount of amyloid removal is an important goal to increase the probability of cognitive improvement and clinical response. Recent findings from the DIAN-TU-001 double-blind period showed that gantenerumab reduced amyloid plaques in a dose-dependent fashion. The effect of gantenerumab on amyloid removal assessed by PiB-PET was more pronounced at higher doses (1200 mg gantenerumab [G3 formulation]). In addition, the data suggested that higher doses resulted in larger treatment effects in downstream biomarkers such as CSF total tau and CSF ptau181 (Salloway et al., 2021).

Thus, the higher doses to be administered in DIAD during the OLE period (up to 1500 mg Q2W) are expected to be more effective on plaque reduction and on downstream biomarkers (i.e., decreased CSF measures of tau and neurodegeneration).

During the DIAN-TU-001 double-blind period, the safety profile of gantenerumab was consistent with trials in sporadic Alzheimer's disease, and no new safety issues were identified. Adverse events reported more frequently (> 20%) with gantenerumab than placebo were injection-site reactions, nasopharyngitis, and back pain; however, most AEs were of mild intensity and not limiting the maintenance of participants in the long-term treatment trial.

Amyloid-related imaging abnormalities (ARIAs) events also represent an adverse event of concern in the development of immune-therapeutics targeting Aβ in the brain (Sperling et al., 2012). These changes may include micro-hemorrhage (MCH), superficial siderosis (SS), and vasogenic edema/effusion (ARIA-E). During the DIAN-TU-001 placebo-controlled period, ARIA-E events were observed in 19.2% (10/52) of the gantenerumab group. ARIA-E findings were mostly asymptomatic (7/10); if symptoms occurred, they were mild in nature (headache, vertigo and ear pain) and resolved. ARIA-E was more frequent during symptomatic stages of the disease (6/10, CDR>0), and at the higher doses (8/10, 900mg-1200mg [G3 formulation]). The mean time for ARIA-E resolution was 10.4±6.2 weeks. ARIA-E events did not increase the probability of participant discontinuation.

In the OLE phase of Studies WN25203 and WN28745, gantenerumab G3, in doses of up to 1200 mg SC Q4W for up to approximately 4.5 years was safe and well tolerated by patients with AD. Refer to the IB for more information on the risk/benefit profile of gantenerumab.

CCI [redacted]

CCI [redacted]

Based on the experience with gantenerumab in the double-blind and OLE period, DIAN-TU-001 will continue with dedicated monitoring and action plans for ARIA during the OLE period. This includes a slow dose titration over 15 months and an ARIA-E risk minimization plan including frequent MRI monitoring and reads by independent experts together with an ARIA-based dose intervention algorithm, which appears to be effective in preventing clinical sequelae to the participants treated with gantenerumab. In addition, sentinel safety MRI cohorts have been added for an initial, early review and safety check at each of the two titration steps at doses higher than those previously tested, i.e., CCI [redacted]

Given results from the GRADUATE studies in early symptomatic sporadic AD, an interim analysis is planned to be conducted in this DIAN-TU-001 OLE in order to inform next steps (for details, see Section 4.1.4).

Given the safety results and biomarker effects discussed above, the risk/benefit ratio for gantenerumab administration at higher doses in the OLE period remains acceptable.

1.7 Drug-specific Study Design

Drug-specific, open-label extension study design features include the use of [^{11}C]PiB-PET as the primary biomarker endpoint. In addition, there is an increased frequency of safety MRI scans during the dose escalation period, and then every 3 to 6 months thereafter, based on available clinical safety data from treatment trials with gantenerumab. Specific action plans that include dose modification should ARIA occur are provided (for details, see Section 1.14).

1.8 Rationale for Biomarker Endpoint

Rationale for change in amyloid load as measured by [^{11}C]PiB-PET composite standardized uptake value ratio (C-SUVR) as biomarker endpoint for DIAN-TU Gantenerumab Arm (Double-Blind and OLE Periods)

Studies show that mutation carriers eligible for enrollment in this study are likely to have abnormal levels of brain amyloid as measured by [^{11}C]PiB binding (Bateman et al., 2012). Statistically significant reductions in [^{11}C]PiB binding were observed in patients treated with gantenerumab as compared to controls with prodromal to moderate (sporadic) Alzheimer's disease with the group reaching <20 centiloids by Week 104 (Klein et al., 2019). Statistically significant reductions in [^{11}C]PiB binding were observed in patients treated with gantenerumab

as compared to controls in the DIAN-TU-001 double-blind placebo-controlled period (Salloway S, 2021).

1.9 Primary Efficacy Endpoint

1.9.1 Double-Blind Period

As detailed in prior protocol versions, the primary efficacy endpoint for the double-blind period was the DIAN-MCE which consisted of 4 cognitive measures: 1) The Delayed Recall score of the International Shopping List Test, 2) The Delayed Recall score of the Logical Memory IIa subtest from the Wechsler Memory Scale-Revised, 3) The Digit Symbol Substitution Test total score from the Wechsler Adult Intelligence Scale-Revised, and 4) The Mini-Mental State Examination total score.

1.9.2 Open-Label Extension

Primary endpoints for the OLE include cerebral amyloid imaging using [^{11}C]PiB-PET as well as the safety and tolerability of treatment with gantenerumab at higher doses.

Additional study endpoints for the gantenerumab OLE will be specified in the gantenerumab-specific SAP. The objectives of the OLE are as follows:

(i) To enable participants, who have committed as much as 4 to 7 years to the double-blind treatment period of the study, to continue or begin to receive gantenerumab, which improves critical markers of their progressive disease, following their participation in the longest placebo-controlled trial in DIAD;

(ii) To determine if continued treatment with gantenerumab at its target dose can result in complete removal of brain amyloid;

(iii) To investigate which non-amyloid related downstream biological measures (e.g. tau and markers of neurodegeneration) can be improved or normalized with complete removal of amyloid at different stages of disease;

(iv) To investigate the relationship of these biological measures with cognitive and clinical findings; and

(v) To assess the summation of gantenerumab's effect on biomarkers during the entire double-blind period and open label extension period, including the common close portion in which biomarkers were not assessed (i.e., from year 4 to 7).

1.10 Additional Endpoints and Biomarker Endpoint for Interim Analyses

Additional endpoints are described in the main study protocol and will be specified as secondary and/or exploratory in the gantenerumab-specific SAP. Refer to the gantenerumab-specific SAP for drug-specific differentiation of endpoint classification based on the respective drug's target and mechanism of action.

1.11 Primary Safety Endpoints

This study will assess safety and tolerability of treatment with gantenerumab in individuals at risk for and with DIAD. The primary safety endpoints for the double-blind period and OLE are identical for all study compounds and are listed in the main study protocol.

Particular safety focus in the gantenerumab arm will be given to ARIA and injection site reactions. However, given the still limited database available today, safety monitoring includes all general safety monitoring parameters, including those for vital signs and ECGs, clinical chemistry and hematology, urinalysis and any AEs.

1.12 Drug-specific Tests

1.12.1 Pharmacokinetics (PK)

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[redacted]

The procedures for the collection, handling and shipping of PK and ADA samples are specified in the central laboratory manual as well as the *Global Manual of Operations* supplied to the site by the sponsor. Please refer to the Laboratory Manual for details on blood volume taken for pharmacokinetic and ADA assessments.

1.13 Drug-specific Safety Concerns

1.13.1 Amyloid related imaging abnormalities (ARIA)

ARIA that can occur as either cerebral edema (ARIA-E) or as hemorrhages (ARIA-H), have been reported with treatment with gantenerumab (Sperling, Salloway et al. 2012). MRI scans will be analyzed for ARIA changes at the Mayo Clinic Aging and Dementia Imaging Research (Mayo-ADIR). The number of microhemorrhages (ARIA-H, including both hemorrhages and hemosiderin deposits) and size of areas of edema (ARIA-E) will be monitored at entry and throughout the trial. Any occurrence of ARIA-E will trigger an acute blood (plasma) collection and collection every 4 weeks thereafter to monitor biomarker changes until the occurrence resolves. In addition, blood will be collected from all participants approximately every 12 weeks to identify biomarkers that correlate with, or are predictive of, ARIA-E. Incidence with associated risks of ARIA on therapy will be compared to placebo findings.

A report of new ARIA changes in a participant will trigger a review by the DIAN-TU Medical Director or designee, Project Arm Leader (PAL), and site principal investigator. No further dosing will occur until this review is completed. This review will include contact with the participant or caregiver to assess for any symptoms associated with the changes and discussion with the central readers. The PAL, as a site independent neurologist, will help ensure consistency of decisions within a study drug arm across sites during the study. See tables in Section 1.14 for ARIA algorithms. The DIAN-TU Medical Director will ensure consistency across study drug arms and will have final decision-making authority on changes in dosing of study drug or safety monitoring; this decision should be received by the site within 7 days of the report of the new ARIA changes, but no later than the day prior to the planned administration of the next dose of medication. A similar process will be followed if a follow-up MRI shows worsening of a previously reported ARIA. The schedule of visits includes frequent MRI scans to assess for ARIA changes.

Safety MRIs will be performed at the same field strength throughout the study, and if possible, on the same scanner. All MRIs will be centrally read.

The MRI schedule may be changed according to the ARIA-related dosing intervention algorithm (see tables in Section 1.14) or per individual request by the site principal investigator or delegated sub-investigator, Project Arm Leader (PAL), or Medical Director or designee.

Refer to prior amendments for details regarding the MRI schedule relative to dosing in the double-blind period.

For the OLE Period, all participants will have Safety MRIs performed (Figure 1) at the following time points:

- Titration Period: prior to each up-titration

- Once at the target dose of [redacted] (or highest dose a participant reaches in case of safety issues): approximately every [redacted] doses (approximately every [redacted] weeks) for the first year at that dose; refer to schedule of events for exact timing.
- The first annual OLE visit will occur at Week 48 after the third dose of [redacted] to obtain the annual/safety MRI prior to subsequent up-titration. In cases where approval and consenting to Amendment 11 does not occur prior to a participant reaching Week 48, initiation of up-titration should occur once consent has been signed and per approved titration and MRI schedule once reviewed by the medical monitoring team.

The first 20 participants to dose at each of the two additional titration steps beyond [redacted] will have an additional safety MRI after the first two [redacted] doses (sentinel safety cohort) at each titration step as follows:

- [redacted]

The DIAN-TU Medical Monitors will perform a safety review of the sentinel cohort data to ensure no issues or concerns are detected, and ensure there are no findings that would warrant additional scanning of additional participants.

1.13.2 Injection site reactions

Injection site reactions after subcutaneous administration have been observed in up to one-third of participants. These reactions are mainly characterized as injection site erythema and rash. It is likely that the injection site reactions may be at least partly related to the injection volume. The majority of events have been mild.

1.13.3 Neutropenia in the gantenerumab OLE period

A potential risk of neutropenia with gantenerumab has been observed in a nonclinical mouse study, as has been described in the IB, but has not been observed in nonclinical cynomolgus monkey study or clinical trials, including at the current human target dose levels (based on a total exposure to gantenerumab G3 and G4 product at any dose of approximately 2500 participants [healthy volunteers or AD patients]). Therefore, the frequency of chemistry and hematology laboratories will be increased from annually after year one (OLE V13) to every 6 months thereafter.

The DSMB meeting frequency will be increased from the originally planned every 6 months to quarterly.

The DIAN-TU Medical Monitors will perform quarterly aggregate review of all safety data (MRI findings, AEs, clinical labs, etc.), in addition to review of all MRIs with any change, as is current practice as outlined below in Section 1.14.

1.14 ARIA-Related Interventions Including Dose Changes and Discontinuation

See main protocol Sections 3.6, 6.1.15, and 6.1.16 for details of MRI reading and reporting. The Mayo-ADIR Clinic will review MRIs and provide a report on ARIA-E and ARIA-H. This report will include both definite and possible findings. A report of new definite ARIA changes in a participant will trigger a review by the Medical Director or designee, PAL, and site principal investigator or delegated sub-investigator. The site principal investigator or designated sub-investigator, in conjunction with the appropriate PAL and the DIAN-TU Medical Director or designee, will review new ARIA findings and apply the intervention algorithms below using best clinical judgment to weigh the data available to decide whether changes in drug treatment are indicated.

ARIA-related intervention algorithm

The tables below detail the ARIA-E linked intervention algorithm based on these scores (Table 1 and Table 2) and the intervention algorithm for ARIA-H microhemorrhage (Table 3) and superficial siderosis (Table 4). Algorithms are based on definite ARIA findings only. For ARIA-E, the algorithm relies on measures of the largest diameter of any ARIA-E. For ARIA-H, areas of microhemorrhage are counted and larger areas of hemorrhage (macrohemorrhage) are noted. Should both ARIA-E and ARIA-H be present in the same participant, the more conservative procedure should be followed.

For ARIA cases where there are symptoms that are possibly related to the ARIA findings, more stringent procedures should be considered (e.g., withhold treatment for symptomatic cases even if the procedures in the table would not require it).

Table 1 Procedures for Asymptomatic ARIA-E

Number of New Occurrences[1]	Dose Adjustment	MRI Monitoring
Any new individual lesions ≤ 2 cm	Continue current dose; do NOT titrate up. If stable or decreased on subsequent MRI, continue study drug at the same dose but do NOT titrate up. Once resolved, up titration may resume. An appropriate dosage may be resumed based on discussion between the site PI or designated sub-investigator, PAL, and Medical Director or designee, at minimum.	Every 4 weeks until resolved

Number of New Occurrences[1]	Dose Adjustment	MRI Monitoring
Any new individual lesions > 2 cm	Follow the Symptomatic ARIA-E guidance.	Follow the Symptomatic ARIA-E guidance

[1] Based on new definite ARIA findings (excluding baseline incidences)

Table 2 Procedures for Symptomatic ARIA-E: Any incidence of symptomatic ARIA-E or asymptomatic with lesions >2 cm

Step-wise Response	Dose Adjustment	MRI Monitoring
Initial action	Suspend/hold dosing.	Every 4 weeks until resolved
Once symptoms and ARIA-E resolve	Restart study drug at an appropriate dosage based on discussion between the site PI or designated sub-investigator, PAL, and Medical Director or designee, at minimum.	4 weeks after dosing restart
If no new MRI findings after dosing restart and MRI	Resume up titration per protocol. An appropriate dosage may be resumed based on discussion between the site PI or designated sub-investigator, PAL, and Medical Director or designee, at minimum.	Resume MRI monitoring per protocol

Note: Asymptomatic lesions > 2 cm are based on measurements of new definite ARIA findings

Table 3 Procedures for ARIA-H Microhemorrhage

Number of New Occurrences[1]	Dose Adjustment	MRI Monitoring
5-9 new, cumulative occurrences[2]	Continue current dose and titration schedule.	MRI 4 weeks later then continue MRI monitoring per protocol
10-15 new, cumulative occurrences	Suspend/hold dosing until stable upon MRI. An appropriate dosage may be resumed based on discussion between the site PI or designated sub-investigator, PAL, and Medical Director or designee, at minimum.	Every 4 weeks until stable
>15 new, cumulative occurrences	A dosing and safety monitoring plan for the participant to be developed by the Site PI, PAL, and Medical Director or their designees based on a thorough safety review. If dosing is discontinued, the participant will be encouraged to complete other assessments and visits per protocol.	MRI 4 weeks later with further MRI monitoring based on the safety monitoring plan developed for the participant

[1] Based on new definite ARIA findings (excluding baseline incidences)

[2] MRI 4 weeks after each new occurrence between 2-4 microhemorrhages, i.e., 2, 2 to 3, 3 to 4.

Table 4 Procedures for Superficial Siderosis

Number of New Occurrences[1]	Dose Adjustment	MRI Monitoring
1 new occurrence of superficial siderosis	Continue dosing at the participant's current dose; do NOT titrate up.	MRI 4 weeks later then continue MRI monitoring per protocol
2-3 new occurrences of superficial siderosis	Stop/hold dosing until MRI 4 weeks later. If additional MRI shows no new lesions, an appropriate dosage and MRI monitoring frequency may be resumed based on discussion between site PI or designated sub-investigator, PAL, and Medical Director or designee, at minimum.	MRI 4 weeks later then continue MRI monitoring per protocol
> 3 new occurrences of superficial siderosis	Consider discontinuation of dosing for the remainder of the trial but continue participation and completion of other assessments and visits per protocol.	MRI 4 weeks later with further MRI monitoring per the safety monitoring plan developed for the participant

[1] Based on new definite ARIA findings (excluding baseline incidences)

ARIAs may be reported as an AE per MedDRA-preferred term based upon investigator's discretion upon review of the MRI finding, assessment of clinical symptoms, and adverse event definitions as outlined in Section 7.1.1.

1.15 Drug-specific Discontinuations or Withdrawal

Decisions regarding participants who have ARIA AEs will be made based on both imaging and clinical factors; decisions will be made by the Medical Director and/or designee following discussion between site principal investigator or designated sub-investigator, and the PAL using the guidelines outlined above in Tables 1-4.

If for any reason participants are unable to up-titrate, e.g. safety concerns, appropriate stable doses for those participants will be determined by the site investigator along with the PAL, Medical Director or designee, as appropriate.

For participants administered [^{18}F]AV-1451 tau PET tracer who exhibit hypersensitivity to [^{18}F]AV-1451 or any of its excipients are to be discontinued from receiving further [^{18}F]AV-1451 tau PET tracer and are **not** to have another [^{18}F]AV-1451 dose administered.

2 STUDY DRUG

Details regarding use in the open-label extension period are outlined below; refer to prior amendments for double-blind period study drug details.

2.1 Open-Label Extension: Drug Description

In the open-label extension period (OLE), participants will be dosed with the gantenerumab G4 formulation. Gantenerumab (RO4909832) G4 Q4W is a recombinant human anti-Aβ monoclonal antibody of the immunoglobulin subclass G1 (IgG1) that binds specifically to aggregated Aβ. CCI [redacted]

The gantenerumab drug substance process was optimized during development to increase process yields and/or manufacturability, leading to the G1, G2, G3 and G4 processes. In addition to extensive analytical comparability assessments, rat studies have been conducted to compare the pharmacokinetics (PK) of G2 versus G1 as well as G4 versus G3. In addition, all these materials have been evaluated with regards to plaque binding in PS2APP transgenic mice. Lastly, a relative bioavailability study comparing G3 and G4 gantenerumab (WP40052) has been completed. Currently there is one phase II study, WN29722 (Graduation), and two Phase III studies, WN29922 (Graduate 1) and WN39658 (Graduate 2) ongoing, in which gantenerumab drug substance G4 is being used.

Gantenerumab is provided as a sterile, preservative-free high concentration liquid formulation CCI [redacted]

2.2 Open-Label Extension: Drug Treatment Regimen

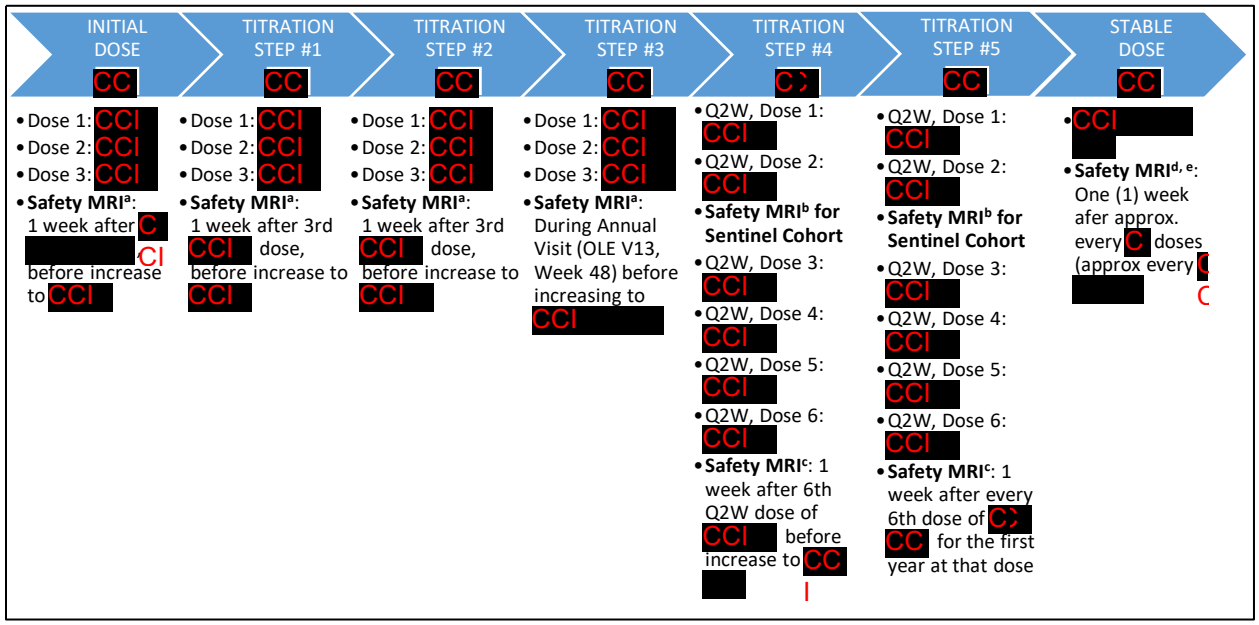
All participants participating in the OLE will receive gantenerumab produced with the G4 process. The pharmacokinetic behavior of the old (G3) and the new (G4) process were compared in a relative bioavailability study. The plasma exposure in terms of AUC_{Inf} was approximately 1.18-fold higher after SC administration of 600 mg gantenerumab G4 compared to 600 mg gantenerumab G3, whereas C_{max} were similar. Based on these results, the dosing regimen of the Phase III program in sporadic AD (WN29922 and WN39658) has been adjusted by a factor of 1.18.

In DIAN-TU-001, all OLE participants will restart titration, starting at a dose of CCI of drug product administered SC approximately every CCI

Participants will initiate up-titration following 3 doses at the CCI level and a safety MRI approximately 1 week after the CCI dose of CCI . Participants will receive at least 3 doses at each titration step, CCI (±C days) apart, before proceeding to the next titration step. Advancement to the next titration step is guided by the ARIA-related intervention algorithm for dose titration (see tables in Section 1.14). The dose titration and safety MRI schedule is provided in Table 5. The target maximum dose for all participants is CCI CCI . Participants will dose escalate/titrate up to CCI receiving at least 3 doses at each titration step. After three (3) doses at CCI apart, participants will continue to escalate to CCI for 6 doses and then to the maximum target dose of CCI

Participants will continue dosing for up to 156 weeks. The total number of doses may vary by participant based on dosing compliance and/or ARIA intervention.

Table 5 DIAN-TU-001 Gantenerumab OLE Titration Safety MRI Schedule



[a] OLE safety MRI schedule. A safety MRI will be scheduled 1 week (± 4 days) after the third dose of each CCI titration step CCI unless otherwise indicated by the ARIA-E and ARIA-H management algorithms (Section 1.14). If an annual visit follows the third dose of a titration step, the annual MRI assessment can fulfill this requirement as long as the MRI reading is reviewed prior to dosing at that visit.

[b] Sentinel safety cohort. The first 20 participants to complete the first two doses at CCI and CCI must complete a safety MRI after two doses at each dose level as part of the sentinel safety cohort before additional participants may dose titrate to that dose level. Safety MRI data will be reviewed and cleared before additional participants will be allowed to up-titrate to each of the higher dose levels.

[c] A safety MRI will be scheduled 1 week (± 4 days) after the sixth dose of each CCI titration step CCI CCI unless otherwise indicated by the ARIA-E and ARIA-H management algorithms (Section 1.14). If an annual visit follows the third dose of a titration step, the annual MRI assessment can fulfill this requirement as long as the MRI reading is reviewed prior to dosing at that visit.

[d] Once at stable dose of CCI, safety MRIs will be scheduled 1 week (± 4 days) after every 12th dose (or approximately every 6 months) for the remainder of the trial unless otherwise indicated by the ARIA-E and ARIA-H management algorithms (Section 1.14).

[e] The titration schema was designed to reach the target dose of CCI; however, the target dose may not be achieved as otherwise dictated by ARIA-E and ARIA-H management algorithms (Section 1.14) or more conservative action by the site principal investigator/DIAN-TU Medical Monitors. Once a participant reaches their stable dose (defined as the maximum dose the participant will remain at for the duration of the trial) safety MRIs will follow every 12 doses (or approximately every 6 months) unless otherwise indicated by the algorithm.

NOTE: The annual/volumetric MRI assessment can fulfill the safety MRI assessment as long as the MRI reading is reviewed prior to dosing at that visit.

Participants should receive at least C doses at each titration step CCI weeks (± 4 days) apart, and C doses at CCI 2 weeks (± 3 days) apart, before proceeding to the next titration step (Table 5). The titration schema was designed to reach the target dose of CCI administered every CCI; however, the target dose may not be

achieved as otherwise dictated by the ARIA-E and ARIA-H management algorithms (Section 1.14) or more conservative action by the site principal investigator/DIAN-TU Medical Monitors.

Participants consenting to Amendment 11 of this protocol and initiating titration beyond CCI [redacted] after having received more than 3 doses of CCI [redacted] may not align with the referenced week numbers in Table 5 or the Schedule of Visits and this will be considered allowable for this study.

2.3 Open-Label Extension: Packaging, Preparation and Administration of Drug Product

The drug product formulation consists of a sterile, preservative-free, solution for subcutaneous injection in a single-use Type 1 glass vial(s). The formulation contains CCI [redacted]

The drug product should be stored at 2-8°C (36-46°F). Exposure of the drug product to direct sunlight in the vial or disposable syringe should be avoided. Do not shake and do not freeze vial contents. Gantenerumab must be prepared for dosing under appropriate aseptic conditions. After transfer to the syringe, the dose solution should be used immediately, but must be used within 2 hours. If the preparation has taken place in an appropriate laminar flow hood (or equivalent), the dose solution in the syringe may be stored for up to 24 hours at 2-8°C (36-46°F) prior to administration, including a maximum of 4 hours at room temperature. All drug product solutions should be brought to room temperature prior to administration to minimize discomfort during administration. Refer to the *Pharmacy Manual* for full storage, vial quantities, dose preparation, and administration instructions.

The investigator or designee is responsible for administering the drug product to the participant, verifying that instructions are followed properly, maintaining accurate records of drug product dispensing and administration, and returning all unused or used drug product supplies to the trial sponsor's designee or destroyed locally with Sponsor approval. Drug product reconciliation must be completed and documented prior to destruction. Refer to the *Pharmacy Manual* and *Global Manual of Operations* for additional details.

Parenteral drug products should be inspected visually for cloudiness, haziness, and particulates prior to administration; partially used vials should NOT be re-used.

Other parenterally administered medications should not be mixed with the drug product.

Clinical study materials will be labeled according to the country's regulatory requirements.

Site staff preparing and administering the drug product should contact the trial sponsor or designee as soon as possible if they have a complaint or problem with the drug product so that the situation can be assessed.

2.4 Open-Label Extension: Blinding of Drug Product

Drug product administered to participants in the OLE will not be blinded.

2.5 Open-Label Extension: Dispensing of Drug Product

The drug product for OLE doses of CCI and above will be administered SC with either a disposable syringe(s) or syringe infusion pump after withdrawal of the drug product from the vial(s). The amount of the dose will be dependent on where the participant is at in the dose titration schedule (Table 6).

The CCI doses will be manually administered with a disposable syringe(s). The drug product will be administered as CCI injection(s) for a total of CCI mL in the abdominal area. Refer to the *Pharmacy Manual* for full dose preparation and administration instructions. The contents of a single syringe should be administered within 10 seconds and all administrations (i.e., when the participant receives two injections) should be completed within 1 minute.

Doses of CCI or higher will be administered by syringe infusion pump. The syringe infusion pump is prepared by drawing up the contents of the required number of vials into a CCI disposable syringe (Table 6). The drug product is slowly administered subcutaneously over a flow rate of 40 mL/hour in the abdomen, alternating location each dosing day. The infusion rate can be slowed if there are signs of intolerance.

Refer to the *Pharmacy Manual* for full dose preparation and administration instructions.

Table 6 Gantenerumab - Formulation Dosing Table

Dose (mg)	Prescribed Volume (mL)	Number of Vials Needed[1]	Administration Route
CCI	CCI	1	Disposable Syringe (1 injection)
CCI	CCI	1	Disposable Syringe (1 injection)
CCI	CCI	2	Disposable Syringe (2 injections)
CCI	CCI	4	Syringe Infusion Pump
CCI	CCI	6	Syringe Infusion Pump

[1] Refers to the number of vials required to be dispensed in order to prepare the appropriate dose due to syringe and pump fill administration needs. Refer to the Pharmacy Manual for full dispensing, preparation, and administration instructions.

Participants will be observed for at least 2 hours after dosing for the first 4 doses. After the 4th injection visit, the observation time may be reduced to at least 1 hour.

Drug product administration as well as post-injection observation will be done by a qualified research nurse who is also equipped with an epinephrine/adrenaline injection.

Note that all cognitive scales are to be administered before administration of drug product.

2.6 Open-Label Extension: Assessing Compliance with Drug Product

Strict adherence to the planned dose regimen is required. However, a single missed dose may not automatically result in removal from the study. Site staff or designee will document completion of injection on study documents. Because all dosing is supervised by trained healthcare providers, participants who successfully receive at least 70% of a dose (e.g., a complete dose not administered due to technical complications) are automatically considered compliant with treatment.

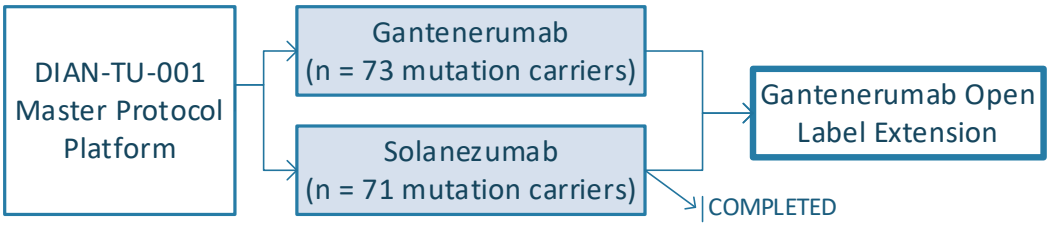
3 STUDY PROCEDURES

3.1 Enrollment

Refer to prior protocol amendments for details associated with randomization into the double-blind period; see details in Section 3.4 of the main protocol.

After completion of the double-blind period, both the gantenerumab and solanezumab arms were analyzed and it was determined that the gantenerumab OLE period would proceed with enrollment. Any participant from either the gantenerumab or solanezumab blinded drug arms is eligible to enroll in the OLE period once confirmed as a mutation carrier, and having met the continuing eligibility requirements outlined in OLE V1 procedures (Section 3.2.1). Eligible participants were able to start treatment in the OLE period after the final analysis of the double-blind treatment period had been completed.

Figure 2 Enrollment Diagram: DIAN-TU-001 Gantenerumab Open Label Extension Period



3.2 Specific Study Visits – Open-Label Extension Treatment Period

The open-label extension (OLE) period procedures to be completed at each study visit are listed below, and provided in the series of tables "Gantenerumab Schedule of Visits: Open-label Extension" at the end of this appendix. Refer to prior amendments for the double-blind visit schedules.

The frequency for safety MRIs is provided in Figure 1 and Table 5.

All information on timing of visits refers to calendar days. The specific date during the first visit (OLE V1) that the first dose of open-label study drug is administered should be used to

determine the timing of all subsequent visits. The dose and treatment regimen are detailed in Section 2.2.

All OLE participants and study sites will be kept blinded to prior drug assignment until the end of OLE to protect study integrity.

Procedural requirements are outlined in Section 6 of the main protocol with the cognitive batteries to be used in the gantenerumab OLE period detailed below for reference. Supporting details for all assessments can be found in the *Global Manual of Operations* and the *DIAN-TU Cognition Core Procedures Manual for OLE.*

Complete Cognitive Battery (Annual Visits)

The Complete Cognitive Battery is performed annually at the DIAN-TU site.

Cognitive measures to be obtained at the OLE V1 and annual visits in the OLE period are administered at a DIAN-TU site and include the iPad-administered and conventional cognitive tests listed below.

- **iPad-administered Cognitive Testing:**
    - International Shopping List Test (12-Item Word List Learning): 3 learning trials, Immediate Recall, 30-min Delayed Recall (Cogstate)
    - Groton Maze Learning Test*: Timed Chase Task, 5 learning Trials, Immediate Recall, 30-min Delayed/Reversed Recall (Cogstate)
    - Cogstate Detection Task
    - Cogstate Identification Task
    - Cogstate One Card Learning Test
    - Cogstate One-Back Task
    - Behavioral Pattern Separation Object Task*
    - Memory Complaint Questionnaire (MAC-Q) *
- **Conventional Cognitive Testing:**
    - Trailmaking Test parts A & B
    - Wechsler Memory Scale-Revised (WMS-R) Digit Spatial Span Forward and Backward
    - Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit-Symbol Substitution Test
    - Raven's Progressive Matrices (Set A)
    - Category Fluency (Animals & Vegetables)
    - WMS-R Logical Memory/Paragraph Memory (Immediate & Delayed Recall)

*These tests should not be administered at any visit to participants who had a CDR of 1 at their original baseline (V2) visit from the double-blind period.

Cognitive Battery Subset (OLE treatment months 6, 18, and 30)

The Cognitive Battery Subset is performed at the visit associated with approximately 6, 18, and 30 months and include the iPad-administered and conventional cognitive tests listed below.

- **iPad-administered Cognitive Testing**
  - International Shopping List Test (12-lteм Word List Learning): 3 learning trials, Immediate Recall, 30-min Delayed Recall (Cogstate)
  - Groton Maze Learning Test: Timed Chase Task, 5 learning Trials, Immediate Recall, 30-min Delayed/Reversed Recall (Cogstate)*
  - Cogstate Detection Task
  - Cogstate Identification Task
  - Cogstate One Card Learning Test
  - Cogstate One-Back Task
- **Conventional Cognitive Testing:**
  - Trailmaking Test parts A & B
  - WMS-R Digit Spatial Span Forward and Backward
  - WAIS-R Digit-Symbol Substitution Test
  - WMS-R Logical Memory/Paragraph Memory (Immediate & Delayed Recall)

*These tests should not be administered at any visit to participants who had a CDR of 1 at their original baseline (V2) visit from the double-blind period.

3.2.1 OLE Visit 1 (baseline/first dose)

Location: DIAN-TU site.

Time/Timing: Approximately a 2 to 3 day visit that is scheduled after the decision is made to continue the drug arm in the OLE. If possible, the study partner should accompany the participant to the DIAN-TU site for this visit. For participants who live near the study site, these visit procedures may be scheduled over a longer time period of up to 2 weeks. If this is not possible, the study partner procedures can be completed via telephone. The sequence and timing of visit procedures is very important. Requirements and suggested timing of events are detailed in the *Global Manual of Operations*.

Note: The date during OLE Visit 1 when the first dose of study drug is administered should be used for determining timing of all subsequent visits.

Procedures:

- Obtain informed consent. Participants who wish to join the OLE may sign informed consent once a decision regarding OLE has been communicated by the sponsor and an approved OLE ICF is available at the site. This will enable ample time for review and consideration of the consent, and genetic counseling prior to dosing in the OLE.

- The following must be confirmed for the participant to be eligible for the OLE:
  (i) participated in the double-blind period,
  (ii) has a confirmed trial-eligible pathogenic DIAD variant,
  (iii) in the opinion of the investigator and sponsor, treatment is not contraindicated for safety,
  (iv) is capable of receiving drug and appropriate clinical safety assessments
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature), weight and height
- Concomitant medication review
- Adverse event assessment
- Administration of C-SSRS
- 12-lead ECG; the ECG should be performed locally
- Blood collection for the following:
  - Clinical laboratory tests (hematology, chemistry, urinalysis)
  - Serum pregnancy test for people of childbearing potential (POCBP)
  - CCI [redacted]; stored plasma and serum
- Physical and neurological examination
- Clinical assessments:
  - Clinical Dementia Rating (CDR) including calculation of Clinical Dementia Rating Sum of Boxes (CDR-SB)
  - Assessment of clinical diagnosis and clinician judgment of symptoms
  - CCI [redacted]

  OTE: For each participant, the CDR and assessment of clinical diagnosis should be administered by the same experienced clinician at all visits. Whenever possible the CDR rater should not be involved in other clinical assessments (e.g., MMSE, FAS, GDS, NPI-Q) or in cognitive testing.
- Complete Cognitive Battery (Section 3.2)
- CCI [redacted]
- umbar puncture (LP) should be conducted as close to the participant's double-blind CCI [redacted]
- **Annual MRI** (including structural and functional MRI) **to be performed on 1st day** and uploaded immediately to ensure reading obtained prior to approval for dosing. This

MRI includes safety MRI sequences. ARIA findings on this MRI may affect continued eligibility. MRI should be performed before lumbar puncture, if on the same date.
- Drug product dosing and post-dose monitoring/evaluation as specified in Section 2.5
- Follow-up phone call or brief visit within 24 hours after LP, and no longer than 48 hours later, to review any adverse events.

3.2.2 OLE Visits 2-6, 8-9, 11-12, 14-15, 17-19, 21-22, 24-26, 28-29, 31-32, 34-35, and 37-39

Location: DIAN-TU site or participant's home or other trial-identified location with the trial-designated home health nurse.

***Timing for Q4W dosing**:* Visits as listed below (calculated from day of first dose at OLE Visit 1), with a **visit window of ± 4 days for Q4W dosing**.

Visit No.	2	3	4	5	6	8	9	11	12
Week	4	8	12	16	20	28	32	40	44

***Timing for Q2W dosing**:* Visits as listed below (calculated from day of first dose at OLE Visit 1), with a **visit window of ± 3 days for Q2W dosing**. Visit references below will remain at the Q4W frequency with two time points (weeks) associated with each visit. All visit procedures should be completed at the first time point; the second time point is for dosing and should include assessment of vitals, concomitant medications, and AEs as outlined in the Schedule of Visits.

Visit No.	14	15	17	18	19	21
Weeks	52 & 54	56 & 58	64 & 66	68 & 70	72 & 74	80 & 82

Visit No.	22	24	25	26	28	29
Weeks	84 & 86	92 & 94	96 & 98	100 & 102	108 & 110	112 & 114

Visit No.	31	32	34	35	37
Weeks	120 & 122	124 & 126	132 & 134	136 & 138	144 & 146

Visit No.	38	39
Weeks	148 & 150	152 & 154

Procedures:
- Concomitant medication review
- Adverse event assessment
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature; weight may be obtained approximately every 3 months per Section 6.1.6 of main protocol)
- Urine pregnancy testing for POCBP

- Drug product dosing and post-dose monitoring/evaluation as specified in Section 2.5
- Phone call (required for OLE visit 3; not required at all home/off-site visits but direct site-participant contact should occur at least once every 3 months throughout the study): the DIAN-TU site coordinator calls participant and addresses any concerns, discusses scheduling of safety MRI and next visits, and encourages compliance

3.2.3 OLE Visits 10, 16, 23, 30, and 36

Location: DIAN-TU site or participant's home or other trial-identified location with the trial-designated home health nurse.

***Timing for Q4W dosing**:* Visit as listed below (calculated from day of first dose at OLE Visit 1), with a **visit window of ± 4 days for Q4W dosing**.

Visit No.	10
Week	36

***Timing for Q2W dosing**:* Visits as listed below (calculated from day of first dose at OLE Visit 1), with a **visit window of ± 3 days for Q2W dosing**. Visit references below will remain at the Q4W frequency with two time points (weeks) associated with each visit. All visit procedures should be completed at the first time point; the second time point is for dosing and should include assessment of vitals, concomitant medications, and AEs as outlined in the Schedule of Visits.

Visit No.	16	23	30	36
Weeks	60 & 62	88 & 90	116 & 118	140 & 142

Procedures:

- Concomitant medication review
- Adverse event assessment
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature; weight may be obtained approximately every 3 months per Section 6.1.6 of main protocol)
- Urine pregnancy testing for POCBP
- Blood collection for stored plasma
- Drug product dosing and post-dose monitoring/evaluation as specified in Section 2.5
- Phone call (required for OLE visit 3; not required at all home/off-site visits but direct site-participant contact should occur at least once every 3 months throughout the study): the DIAN-TU site coordinator calls participant and addresses any concerns, discusses scheduling of safety MRI and next visits, and encourages compliance.

3.2.4 OLE Visit 7

Location: DIAN-TU site or participant's home or other trial-identified location with the trial-designated home health nurse.

Timing: 24 weeks ± 4 days from day of first dose at OLE Visit 1.

Procedures:

- Cognitive Battery Subset (see Section 3.2)
- Mini-Mental State Examination (MMSE)
- Concomitant medication review
- Adverse event assessment
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature; weight may be obtained approximately every 3 months per Section 6.1.6 of the main protocol)
- Blood collection for the following:
  - CCI [redacted]
  - Stored plasma
- C-SSRS administration
- Urine pregnancy testing for POCBP
- Drug product dosing and post-dose monitoring/evaluation as specified in Section 2.5
- Phone call (not required at all home/off-site visits but direct site-participant contact should occur at least once every 3 months throughout the study): the DIAN-TU site coordinator calls participant and addresses any concerns, discusses scheduling of safety MRI and next visits, and encourages compliance.

3.2.5 OLE VISITS 13, 27, and 40 or Early Termination: ANNUAL VISIT AT DIAN-TU SITE

Location: DIAN-TU site

Timing: 48 and 104, and 156 weeks ± 7 days (or Early Termination) from day of first dose at OLE Visit 1; approximately a 2- to 3-day visit. The second dose administration for Q2W dosing associated with each visit should be completed at weeks 50, 106, and 158 weeks ± 3 days, respectively, and will include vitals, concomitant medications, and AEs as outlined in the Schedule of Visits. The sequence and timing of visit procedures is very important. Requirements and suggested timing of study procedures are detailed in the *Global Manual of Operations*. For participants who live near the study site, these visit procedures may be scheduled over a longer time period of up to 2 weeks.

Procedures:

- Concomitant Medications
- Adverse Event Assessment
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature); weight and height
- Administration of C-SSRS

- Blood collection for the following:
  - Clinical laboratory tests (hematology, chemistry, urinalysis)
  - CCI [redacted]
- Urine pregnancy testing for POCBP
- Physical and neurological examination
- Clinical assessments:
  - Clinical Dementia Rating (CDR) including calculation of Clinical Dementia Rating Sum of Boxes (CDR-SB)
  - Assessment of clinical diagnosis and clinician judgment of symptoms
  - CCI [redacted]

  OTE: For each participant, the CDR and assessment of clinical diagnosis should be administered by the same experienced clinician at all visits. Whenever possible the CDR rater should not be involved in other clinical assessments (e.g., MMSE, FAS, GDS, NPI-Q) or in cognitive testing.
- Complete Cognitive Battery (see Section 3.2)
- CCI [redacted]
- umbar Puncture (LP) should be conducted as close to the participant's double-blind CCI [redacted]
- Annual MRI (including structural and functional MRI) uploaded immediately to ensure reading obtained prior to dosing. This MRI includes safety MRI sequences. MRI should be performed before lumbar puncture, if on the same date.
- Drug product dosing and post-dose monitoring/evaluation as specified in Section 2.5 for OLE V13 and OLE V27; no drug administration should occur at OLE V40 or an early termination visit.
- Follow-up phone call or brief visit within 24 hours after LP, and no longer than 48 hours later, to review any adverse events.

3.2.6 OLE Visits 20 and 33

Location: DIAN-TU site or participant's home or other trial-identified location with the trial-designated home health nurse.

Timing: 76 and 128 weeks ± 3 days from day of first dose at OLE Visit 1. The second dose administration for Q2W dosing associated with each visit should be completed at weeks 78 and

130 ± 3 days, respectively, and will include vitals, concomitant medications, and AEs as outlined in the Schedule of Visits.

Procedures:

- Cognitive Battery Subset (Section 3.2)
- Mini-Mental State Examination (MMSE)
- Concomitant medication review
- Adverse event assessment
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature; weight may be obtained approximately every 3 months per Section 6.1.6 of the main protocol)
- C-SSRS administration
- Blood collection for the following:
  - Clinical laboratory tests (hematology, chemistry)
  - Stored Plasma
- Urine pregnancy testing for POCBP
- Drug product dosing and post-dose monitoring/evaluation as specified in Section 2.5
- Phone call (not required at all home/off-site visits but direct site-participant contact should occur at least once every 3 months throughout the study): the DIAN-TU site coordinator calls participant and addresses any concerns, discusses scheduling of safety MRI and next visits, and encourages compliance

3.2.7 Safety Follow-up Visit

Location: DIAN-TU site or participant's home or other trial-identified location with the trial-designated home health nurse.

Timing: The end of study safety follow-up visit should be performed 12 weeks (± 7 days) after the last dose of OLE treatment.

Procedures:

- Concomitant Medications
- Adverse Event Assessment
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature; weight may be obtained approximately every 3 months per Section 6.1.6 of the main protocol)
- Clinical laboratory tests (hematology, chemistry, urinalysis at the discretion of the investigator)
- Serum pregnancy testing for POCBP

3.2.8 Early Termination Visit/Post-treatment Follow-up

If a participant withdraws or is terminated from the OLE period prior to completion, every effort should be made to schedule an early termination visit that will include all procedures done at OLE visit 40. Procedures may also be eliminated on a case-by-case basis, as determined by the sponsor. Drug-specific testing should also be obtained at early termination visit only if

prior to completion of V40 at week 156 (see Section 1.12). PET imaging studies may be omitted if early termination occurs less than 6 months after the previous PET imaging or if precluded by local regulations/dosimetry limits. Other procedures may also be eliminated on a case-by-case basis, as determined by the sponsor.

Per the main protocol Section 6.3.7, any participant meeting study drug discontinuation criteria per main protocol Section 4.4.1 due to safety reasons, inability to continue treatment administration/dosing, or perform study procedures, will be encouraged to continue participation in any of the scheduled clinical, cognitive, and/or biomarker assessments that they are able to perform, even though dosing has concluded. The determination of which assessments are to be attempted/completed will be decided by the site principal investigator and sponsor and will be based on the participant's capabilities, the benefit to the study, and the risk associated with continued participation at the time of study drug discontinuation. The level of continued participation may change if/as the participant's status changes.

3.2.9 Safety Magnetic Resonance Imaging MRI

Safety MRIs on 3T scanners will be done primarily to monitor for ARIA. Safety MRI visits will be scheduled over the entire course of the OLE period in addition to the annual MRIs which include safety reads.

Location: Safety MRIs may be done at the DIAN-TU site or, for participants who live at a distance from the host DIAN-TU site, safety MRIs may be performed at an ADNI/ADCS site if possible or at a 3T scanner near the participant's home.

Note: Safety MRI timing may be adjusted based on the ARIA-related intervention steps in Section 1.14 of this appendix including additional MRIs and dosing adjustments for safety.

Procedures: See Section 6.1.16 of the main protocol for more information. Detailed requirements are provided in the *MRI Technical Manual*.

3.2.9.1 Regular Safety MRIs

Timing: Annual MRIs in addition to Weeks 9, 21 and 33 weeks ± 4 days from OLE V1 (calculated from the day of the first dose) during Q4W dosing; and Weeks 59, 71, 83, 95, and 127 weeks ± 3 days from OLE V1 (calculated from the day of the first dose) during Q2W dosing as outlined in Figure 1 and Table 5 in this appendix. Sites must ensure that study visits are scheduled so that MRIs are uploaded and available for central read at least 5 working days before next administration of study product.

Note: Based on when amendment 11 is approved at each site, some participants may commence dose titration above CCI [redacted] after having more than 3 doses at that dose level. In these cases, the medical monitoring team will review the participant's current visit schedule to identify the timing of the MRIs in the same manner as outlined in the schedule of visits however, the exact visit numbers may not align.

3.2.9.2 Sentinel Cohort MRIs

Timing: Two additional safety MRIs will be collected for a sentinel cohort of the first 20 participants receiving doses above CCI [redacted]. Following the 3rd dose of CCI [redacted], the first 20 participants titrating to CCI [redacted] and CCI [redacted] will have an additional safety MRI after the first two doses at each titration step, i.e., the first 20 participants receiving two doses of CCI [redacted] two weeks apart, and the first 20 participants receiving two doses of CCI [redacted] two weeks apart.

4 DRUG-SPECIFIC ANALYSIS PLAN

4.1 OLE Period

4.1.1 Biomarker Endpoint Statistical Analysis, Power and Sample Size Justification

The primary endpoint for the OLE period is PiB-PET composite SUVR.

The null hypothesis for the OLE period is that gantenerumab will not reverse the amyloid growth at the end of 3-year OLE compared to the OLE baseline for all participants who enroll into OLE: H_0: $\mu \geq 0$, where μ is the mean change from the OLE baseline to the end of 3-year OLE in PiB-PET SUVR. The alternative hypothesis is that gantenerumab reverses the amyloid growth: H_a: $\mu < 0$. The change from baseline will be analyzed using mixed model for repeated measures (MMRM) with baseline as a covariate in the model.

4.1.2 Biomarker Endpoint Power Analysis

Based on DIAN-TU-001 data from the double-blind period, the mean (SD) change from the OLE baseline in PiB-PET composite SUVR to the end of the 3-year OLE period with dosing up to CCI [redacted] is projected to be at least -0.473 (0.540) for participants on gantenerumab from the beginning of the double-blind period, and participants starting gantenerumab in OLE (having been on either active solanezumab or placebo) together. The recruitment goal of OLE is to enroll 60 to 90 of the 144 mutation positive participants who participated in the placebo-control period. Assuming an annual dropout rate of 5%, at the end of 3-year OLE, there will be 51 to 77 participants and it will provide over 99% power to detect the projected mean change from baseline using a one-sided one-sample t-test with type I error 0.025.

4.1.3 Biomarker Endpoint Sample Size Justification

Figure 3 **Power estimation for different sample sizes and different projected mean changes from the OLE baseline to the end of the 3-year OLE. One-sided, one-sample t-test with type I error of 0.025**

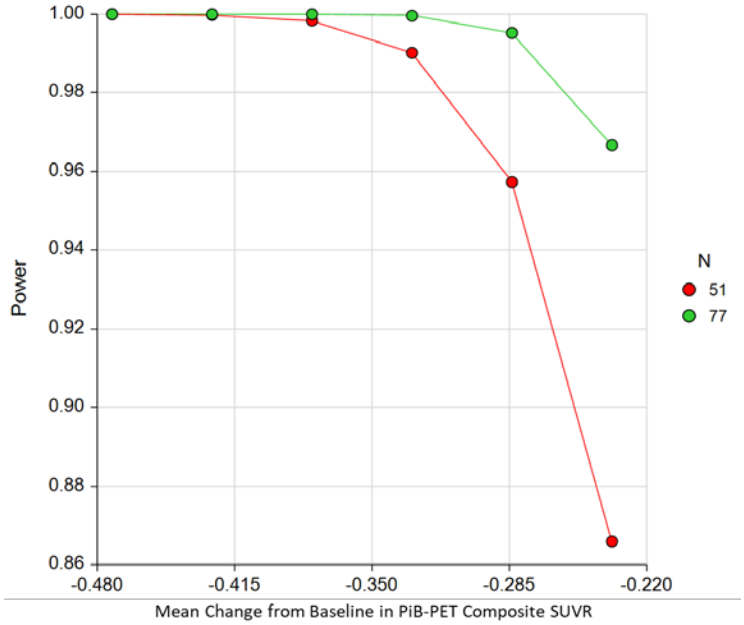


Figure 4 demonstrates that even with the least number of enrolled participants (51), there still is more than 80% power to detect a reversal in amyloid growth from the OLE baseline as small as -0.22 SUVR.

4.1.4 Interim Analysis

CCI [redacted]

4.2 Changes to the Data Analysis

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the final SAP and clinical study report (CSR). Additional analyses of the data will be conducted as deemed appropriate.

5 DRUG-SPECIFIC ADVERSE EVENTS AND REPORTING

No adverse events of special interest are defined.

6 REFERENCES

Bard F et al. (2000) Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. Nat Med 6:916-919.

Bateman RJ et al. (2012) Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 367:795-804.

Bohrmann B et al. (2012) Gantenerumab: a novel human anti-Abeta antibody demonstrates sustained cerebral amyloid-beta binding and elicits cell-mediated removal of human amyloid-beta. J Alzheimers Dis 28:49-69.

Klein G, Delmar P, et al. (2019). Gantenerumab reduces amyloid-β plaques in patients with prodromal to moderate Alzheimer's disease: a PET substudy interim analysis. Alzheimers Res Ther 11(1):101.

Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in Early Alzheimer's Disease. N Engl J Med. 2021 ;384(18):1691-1704. Epub 2021 Mar 13.

Ostrowitzki S et al. (2012) Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol 69:198-207.

Ringman, J. M. et al. Neuropathology of autosomal dominant Alzheimer disease in the national Alzheimer coordinating center database. J. Neuropathol. Exp. Neurol. 75, 284–290 (2016).

Salloway S, Farlow M, McDade E, et al; Dominantly Inherited Alzheimer Network–Trials Unit. A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease. Nat Med. 2021 Jul;27(7):1187-1196.

Schenk D et al. (1999) Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 400:173-177.

Shepherd, C., McCann, H. & Halliday, G. M. Variations in the neuropathology of familial Alzheimer’s disease. Acta Neuropathologica vol. 118 37–52 (2009).

Sperling R et al. (2012) Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. Lancet Neurol 11:241-249.

Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimers Res Ther. 2021 ;13(1):80.

GANTENERUMAB SCHEDULE OF VISITS: OPEN-LABEL EXTENSION

Gantenerumab Schedule of Visits: Open-label Extension

PROCEDURE:	VISIT SITE[1,2]	DIAN-TU	H	H	MRI	H	H	H	MRI	H	H	H	MRI
	Visit No.	OLE V1	OLE V2	OLE V3	OSM 1	OLE V4	OLE V5	OLE V6	OSM 2	OLE V7	OLE V8	OLE V9	OSM 3
	Timing (weeks)[3]	0	4	8	9	12	16	20	21	24	28	32	33
Informed Consent		X[4]											
Verification of Eligibility for OLE[5]		X											
Concomitant Medications		X	X	X		X	X	X		X	X	X	
Adverse Event Assessment		X	X	X		X	X	X		X	X	X	
Hematology, Chemistry, Urinalysis		X											
CCI													
CCI													
Stored Serum and/or Plasma[8]		X								X[8]			
Pregnancy testing[9]		X	X	X		X	X	X		X	X	X	
C-SSRS		X								X			
Vital Signs[10]		X	X	X		X	X	X		X	X	X	
Physical/Neurological Exam		X											
Clinical Assessment: Full Battery[11]		X											
Clinical Assessment: MMSE Only[11]										X			
12-lead ECG[12]		X											
Cognitive Testing[13]		X								X			
Annual/Volumetric MRI		X											
CCI													
Drug Product Administration (mg) [16]		C											
Coordinator Phone Call[17]			X	X		X	X	X		X	X	X	

Gantenerumab Schedule of Visits: Open-label Extension

PROCEDURE:	VISIT SITE[1,2]	H	H	H	DIAN-TU	H	MRI (1st 20)	H	H	H	H	MRI	H	H	MRI (1st 20)	H	H
	Visit No.	OLE V10	OLE V11	OLE V12	OLE V13		SC1 MRI[19]	OLE V14		OLE V15		TOSM CCI	OLE V16		SC2 MRI[19]	OLE V17	
	Timing (weeks)[3]	36	40	44	48	50	51	52	54	56	58	59	60	62	63	64	66
Concomitant Medications		X	X	X	X	X		X	X	X	X		X	X		X	X
Adverse Event Assessment		X	X	X	X	X		X	X	X	X		X	X		X	X
Hematology, Chemistry, Urinalysis					X												
CCI																	
Stored Serum and/or Plasma[8]		X[21]			X								X[21]				
Pregnancy testing[9]		X	X	X	X			X		X			X			X	
C-SSRS					X												
Vital Signs[10]		X	X	X	X	X		X	X	X	X		X	X		X	X
Physical/Neurological Exam					X												
Clinical Assessment: Full[11]					X												
Cognitive Testing[13]					X												
Annual/Volumetric MRI					X												
3T Safety/Titration MR[14]							X					X			X		
CCI																	
CCI																	
Drug Product Administration[16]		CCI															
Coordinator Phone Call[17]		X	X	X		X		X	X	X	X		X	X		X	X

Gantenerumab Schedule of Visits: Open-label Extension

PROCEDURE:	VISIT SITE[1,2]	H	H	MRI	H	H	H	H	H	H	MRI	H	H	H	H	H	H
	Visit No.	OLE V18		TOSM 1500[23]	OLE V19		OLE V20		OLE V21		TOSM 1[20]	OLE V22		OLE V23		OLE V24	
	Timing (week)[3]	68	70	71	72	74	76	78	80	82	83	84	86	88	90	92	94
Concomitant Medications		X	X		X	X	X	X	X	X		X	X	X	X	X	X
Adverse Event Assessment		X	X		X	X	X	X	X	X		X	X	X	X	X	X
Hematology and Chemistry							X[18]										
Stored Plasma[8]							X							X			
Pregnancy Testing[9]		X			X		X		X			X		X		X	
C-SSRS							X										
Vital signs[10]		X	X		X	X	X	X	X	X		X	X	X	X	X	X
Clinical Assessment: MMSE Only[11]							X										
Cognitive Testing[13]							X										
3T Safety/Titration Safety MRI[14]				X							X						
Drug Product Administration[16]		CCI	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coordinator Phone Call[17]		X	X		X	X	X	X	X	X		X	X	X	X	X	X

Gantenerumab Schedule of Visits: Open-label Extension

PROCEDURE:	VISIT SITE[1,2]	MRI	H		H		DIAN-TU	H	H	H	H	H	H	H	H	H	H
	Visit No.	TOSM 2[24]	OLE V25		OLE V26		OLE V27		OLE V28		OLE V29		OLE V30		OLE V31		
	Timing (week)[3]	95	96	98	100	102	104	106	108	110	112	114	116	118	120	122	
Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology, Chemistry, Urinalysis							X										
CCI [redacted]							[redacted]										
[redacted]							[redacted]										
Stored Serum and/or Plasma[8]							X						X[21]				
Pregnancy Testing[9]			X		X		X		X		X		X		X		
C-SSRS							X										
Vital signs[10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical/Neurological Exam							X										
Clinical Assessment: Full[11]							X										
Cognitive Testing[13]							X										
Annual/Volumetric MRI							X										
3T Safety/Titration Safety MR[14]		X															
CCI [redacted]							[redacted]										
[redacted]							[redacted]										
[redacted]							[redacted]										
[redacted]							[redacted]										
Drug Product Administration[16]			CCI [redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Coordinator Phone Call[17]			X	X	X	X		X	X	X	X	X	X	X	X	X	

Gantenerumab Schedule of Visits: Open-label Extension

PROCEDURE:	VISIT SITE[1,2]	H	H	MRI	H	H	H	H	H	H	H	H	H	H	H	H
	Visit No.	OLE V32		TOSM 3[25]	OLE V33		OLE V34		OLE V35		OLE V36		OLE V37		OLE V38	
	Timing (week)[3]	124	126	127	128	130	132	134	136	138	140	142	144	146	148	150
Concomitant Medications		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Hematology and Chemistry					X[18]											
Stored Plasma[8]					X						X					
Pregnancy Testing[9]		X			X		X		X		X		X		X	
C-SSRS					X											
Vital signs[10]		X	X		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Assessment: MMSE Only[11]					X											
Cognitive Testing[13]					X											
3T Safety/Titration Safety MRI[14]				X												
Drug Product Administration[16]		CCI	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coordinator Phone Call[17]		X	X		X	X	X	X	X	X	X	X	X	X	X	X

Gantenerumab Schedule of Visits: Open-label Extension

PROCEDURE:	VISIT SITE[1,2]	H	H	DIAN-TU	H
	Visit No.	OLE V39		OLE V40 / Early Termination	Safety Follow-up Visit
	Timing (week)[3]	152	154	156	12 weeks post last dose
Concomitant Medications		X	X	X	X
Adverse Event Assessment		X	X	X	X
Hematology, Chemistry, Urinalysis				X	X[22]
CCI [redacted]				[redacted]	
[redacted]				[redacted]	
Stored Serum and Plasma[8]				X	
Pregnancy Testing[9]		X		X	X
C-SSRS				X	
Vital signs[10]		X	X	X	X
Physical/Neurological Exam				X	
Clinical Assessment: Full[11]				X	
Clinical Assessment: MMSE Only[11]					
Cognitive Testing[13]				X	
Annual/Volumetric MRI				X	
3T Safety/CCI [redacted]					
[redacted]				[redacted]	
[redacted]				[redacted]	
[redacted]				[redacted]	
[redacted]				[redacted]	
Drug Product Administration[16]		CCI	[redacted]		
Coordinator Phone Call[17]		X	X		

OSM = Open-label Safety MRI visits for 3T Safety/Titration Safety

Footnotes:

1. Annual visits will be conducted at the DIAN-TU site (DIAN-TU). For participants who live at a distance from the DIAN-TU site, other visits may be conducted at a site nearer to their home (H); Safety magnetic resonance imaging (MRI) (OSM visits) will be done at the DIAN-TU site or a qualified imaging center in reasonable proximity to the participant's home for those not close to their DIAN-TU site. When possible, these will be done at an ADNI and/or ADCS site qualified imaging center. See next two footnotes for additional detail.

2. Infusions/injections and safety visits (designated as occurring at home [H]) may occur at the DIAN-TU site or, for participants who live at a distance from the DIAN-TU site, these visits may be conducted by a home health nurse at the participant's home or other trial-identified location. These visits may include phone calls from the host DIAN-TU site staff.
3. The specific date during OLE V1 when the first dose of study drug is administered for the open-label treatment period should be used to determine timing of subsequent visits. OLE V1 takes approximately 2-3 days to complete.
4. The informed consent form (ICF) for the open-label extension (OLE) period must be signed before any study procedures are performed. This can be done once an approved OLE consent is available at the site, i.e., prior to this visit to enable time for consideration and review of the details.
5. Participants must be mutation positive.
6. CCI [redacted].
8. For future studies, including future regulatory inquiries or additional monitoring of anti-drug antibodies, other drug-specific tests or ARIA-E. Additional unscheduled blood collection may occur to monitor ARIA-E, upon discovery and every 4 weeks following until resolution. See main protocol Section 6.1.12.
9. Serum pregnancy testing will be performed at OLE V1 and the safety follow-up visit. Urine pregnancy testing will be performed at all other monthly visits, i.e. every 4 weeks. Pregnancy tests will be confirmed as negative prior to Q4W dosing with study drug, or prior to every other dose when dosing Q2W. Women who have undergone tubal ligation are also required to have pregnancy tests performed. Alternate tests may be used if urine collection is not feasible but must be approved by the sponsor in advance.
10. Blood pressure, heart rate, respiratory rate, and body temperature will be collected at all visits. Height will be measured at OLE baseline (OLE V1) and annual visits only; weight will be measured approximately every 3 months.
11. Clinical assessments: DIAN-TU clinical assessment battery includes: study partner interview and administration of CDR and supplemental CSR-SB; clinician assessment of CCI [redacted]
12. Electrocardiogram (ECG) assessment should be performed locally.
13. See Section 3.2 in this appendix and the arm-specific *DIAN Trials Unit Cognition Core Procedures Manual* for additional details, including visit specific battery information. Cognitive testing should be completed as early in the day as possible, and before study drug infusion or injection.
14. A safety MRI will be scheduled 1 week (± 4 days) after the third dose of each CCI titration steps CCI [redacted], and after the sixth dose of the each CCI titration step CCI [redacted]) unless otherwise indicated by the ARIA-E and ARIA-H management algorithms (Section 1.14). Once at stable dose (after the annual safety MRI at week 104 (OLE V27) following approximately 22 doses of CCI administered CCI), safety MRIs will be scheduled 1 week (± 4 days) after every 12th dose (CCI unless otherwise indicated by the ARIA-E and ARIA-H management algorithms). Additional safety MRIs may be scheduled to monitor ARIA-E events (Section 1.13.1).
15. CCI [redacted]
16. All participants enrolled in OLE for gantenerumab will start at the CCI dose CCI and will up-titrate to CCI [redacted]; then at increased dosing frequency of CCI to a target dose of CCI . Participants should receive at least three doses at each Q4W titration step up to CCI 4 weeks (± 4 days) apart, before proceeding to the next titration step. Participants should receive six doses of CCI 2 weeks (± 3 days) apart before proceeding to the final titration step of

CCI 2 weeks (± 3 days) apart. The titration schema was designed to reach the target dose of CCI administered every 2 weeks; however, the target dose may not be achieved as otherwise dictated ARIA-E and ARIA-H management algorithms (Section 1.14) or more conservative action by the site principal investigator/DIAN-TU Medical Monitors. If needed, the schedule of assessments will be adjusted. Dosing visits occurring every 2 weeks will be identified/labeled as one visit. The first portion of the visit will include completion of any required visit procedures and dosing; two weeks ± 3 days after, the second dose will be administered.

17. Site study coordinators should call participants either during or within two weeks after OLE V2 and OLE V3. For OLE V4 and subsequent home visits, coordinator calls can be made with less frequency at the discretion of the PI or designee, and/or coordinator, and participant, but should occur at least every 3 months.
18. For OLE V20 and OLE V33, chemistry and hematology are required; no urinalysis is needed.
19. A sentinel cohort of the first 20 participants to titrate beyond CCI every C weeks will have an additional safety MRI performed after the first two doses of CCI administered two weeks apart (Week 51, SC1-MRI) prior to up-titrating to CCI ; and after the first CC doses of CCI administered two weeks apart (Week 63, SC2-MRI). The DIAN-TU Medical Monitors will review the individual and aggregate data to ensure there are no safety findings warranting more frequent MRI for all participants.
20. Any participant not having initiated up-titration at any point should use the MRI label of OSM4 for this safety MRI.
21. For plasma collection only at this visit.
22. Clinical laboratory tests (hematology, chemistry, urinalysis) at the discretion of the investigator.
23. Any participant not having initiated up-titration at any point should use the MRI label of OSM6 for this safety MRI.
24. Any participant not having initiated up-titration at any point should use the MRI label of OSM7 for this safety MRI.
25. Any participant not having initiated up-titration at any point should use the MRI label of OSM8 for this safety MRI.